The Relationship Between Repeated Subclinical Head Impacts and Electrophysiological Indices of Brain Function

by

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LIST OF ABBREVIATIONS

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AAN American Academy of Neurology

ADD Attention deficit disorder

ADHD Attention deficit hyperactivity disorder

AE Athletic exposures

ANOVA Analysis of variance

ATP Adenosine triphosphate

BNA Brain Network Analysis

BOLD Blood-oxygen-level dependent

CER Comparative effectiveness research

CISG Concussion in Sport Group

CSF Cerebrospinal fluid

CTE Chronic traumatic encephalopathy

DKI Diffusion kurtotis imaging

DLPFC Dorsolateral prefrontal cortex

DTI Diffusion tensor imaging

EEG Electroencephalogram

EGI Electro-Geodesics Inc.

ERN Event-related negativity

ERP Event-related potentials

FA Fractional anisotropy

FFT Fast-Fourier transformation

FLAIR Fluid attenuated inversion recovery

fMRI Functional magnetic resonance imaging

GLM General linear models

GoC Correct/Go (ERP Condition)

GoI Incorrect/Go (ERP Condition)

GSI Gadd severity index

HBI Health behavior inventory

HIC15 Head injury criterion

HITS Head Impact Telemetry System

HITsp Head Impact Technology severity profile

LME Linear mixed effects

MANOVA Multivariate analysis of variance

MD Mean diffusivity

MRI Magnetic resonance imaging

ms milliseconds

mTBI Mild traumatic brain injury

NMDA N-Methyl-D-aspartic acid

Na-K Sodium-potassium

NgC Correct/No-Go (ERP Condition)

NgI Incorrect/No-Go (ERP Condition)

NIOSHA National Institute for Occupational Safety and Health

Pe Post-error positivity

P-values Probability values

qEEG Quantitative electroencephalograph

RHSI Repeated subclinical head impacts

RSHI Repeated subclinical head impacts

RWECP combined-probability risk-weighted cumulative exposure

SRC Sport-related concussion

SWLS Satisfaction With Life Survey

TBH Time between hits

TBI Traumatic brain injury

TPM Two-photon microscopy

VMPFC Ventral medial prefrontal cortex

ABSTRACT

Background Concussions occur at a rate of seven million annually within high school athletics, where football is responsible for the largest proportion of these injuries among all sports. Literature suggests that both concussion history and exposure to repeated subclinical head impacts may lead to long term declines in brain function. The length of exposure to result in these effects has mostly been observed in adult athletes using very large (e.g. lifetime) windows of exposure. **Objective** The objective of the current study is to investigate changes in ERP components across the course of a season of exposure in contact and non-contact groups of high school athletes. The relationship between any potential changes measured in ERP components and repeated subclinical head impacts within the contact sport group will also be elucidated. **Methods** 24 athletes were included in the study (Twelve football and twelve non-contact athletes). Athletes underwent testing prior to the season, at mid-season and at the end of the season. Event-related potential components were calculated during an auditory Go/No-Go task while participants were equipped with a 256 electrode EEG. Football athletes were also equipped with helmets which recorded the magnitude and frequency of impacts over the course of a season. **Results** Changes in N2 and P3 latency between each athlete type were seen across the course of the season. N2 latency for both athlete types was significantly influenced by the number of previous diagnosed concussions. Within the football athletes, linear impact density was shown to significantly influence changes in P3b that occurred across the season. This measure may help classify contact sport athlete sensitivity to incur concussive injuries. **Conclusion** The results from this study indicate that contact and non-contact athletes show differential changes in brain components over the course of a season of exposure. Changes within the contact group may be explained in part by the magnitude of head impact metrics incurred over that time.

CHAPTER 1

Introduction

Concussions occur at an alarming rate of 1.6 to 3.8 million in the USA annually[1]. The most up to date sports-related concussion definition was provided at the International Consensus on Concussion in Berlin where it was defined as "Sport related concussion is a traumatic brain injury induced by biomechanical forces." Four features were listed as useful in clinically defining sports related concussion (SRC): caused by an impulsive force to the head or body, rapid onset of signs and symptoms, no abnormalities seen in structural neuroimaging, presentation of a range of clinical symptoms, which follow a sequential course[2].

Among the many methods used to evaluate concussions neuroimaging has established itself at the forefront of future technology given its ability to objectively diagnose sequelae[3]. At the current time, neurocognitive testing remains the gold-standard assessment technique[4,5]. Despite its promise, this form of testing is prone to respondent bias which can strongly decrease its criterion-related validity. Ergo, there is appeal in finding a measure which is less dependent on participant candor, yet finding such a measure remains elusive at the current time.

Concussion research has helped elucidate common short term effects which include but are not limited to headache, imbalance, trouble focusing and slowed reaction time[6,7]. However, the current narrative has changed to increasingly focus on the long-term effects of these injuries. Among these long term concerns are chronic trau-

matic encephalopathy (CTE). Although it was originally hypothesized that concussions were the cause of CTE, more recent research suggests that repeated subclinical head impacts (RSHI) are responsible[8]. Indeed, long term effects such as CTE can be present without concussion[8,9]. For this reason, research in this domain has expanded to include RHSIs. At the current time clinical evaluations are insensitive to repeated subclinical head impacts[10], yet changes have been demonstrated utilizing magnetic resonance imaging-based neuroimaging techniques (e.g. diffusion tensor imaging (DTI)[11,12], functional magnetic resonance imaging (fMRI)[13], diffusion kurtosis imaging (DKI)[10]). Although the long-term implications are unknown, these studies have suggested changes can occur in as little as one season of play and may persists over a lifetime.

Although the aforementioned MRI-based techniques have greatly enhanced our current understanding of RHSIs they are not without their disadvantages. Among them are the high cost and, due to its size, inability to perform on field testing. Electrophysiological devices on the other hand are highly portable and could in theory provide additional insight on the field of play. It is also less susceptible to movement artifacts[14]. Several electrophysiological applications are possible[15], yet most were limited in their investigations of RSHIs.

Event-related potential (ERP) components can be divided based on whether they are time-locked to a stimulus presentation (N2, P3b) or a participants response (ERN, Pe). Both stimulus locked and response-locked components have been associated with a variety of cognitive functions. Increasingly positive error related negativity (ERN) values have been associated with deficits in error processing[16]. Whereas increasingly positive error positivity (Pe) have been associated with increases in error awareness[17,18]. In terms of stimulus-locked components, two are commonly seen in the literature: N2 and P3b. Increases in P3b amplitude have been associated

with increases in learning[19–21], achieved task proficiency[22] as well as exercise[23,24]. Similarly, increases in peak N2 amplitude (or increasingly negative N2 amplitudes) have been associated with increases in response inhibition and cognitive control[25,26]. In addition to their proven association with the aforementioned cognitive functions, event-related potentials have demonstrated sensitivity to subclinical alterations following concussion[27]. Thus, ERPs are a prime neuroimaging candidate to evaluate brain alterations following repeated subclinical head impacts.

The goal of the present study therefore, is to further investigate this relationship while using a more direct, rather than self-reported, measure of repeated subclinical head impacts. In accordance with prior work, increases in P3b amplitude and/or shorter latency will be interpreted as increases in information processing[25,28–30]. Similarly, increases in peak N2 amplitude (or increasingly negative N2 amplitudes) will be interpreted as increases in response inhibition and cognitive control[25,26].

1.1 Statement of Purpose

The purpose of this investigation is to retrospectively analyze evaluate the relationship between event-related potentials and head impact metrics incurred during a football season. For the purposes of this investigation we define "impact metrics" as any variables related to the frequency and magnitude of RHSIs.

1.1.1 Hypothesis 1

High school football players with higher impact metrics over the course of a season will demonstrate alterations in electrophysiology (e.g. less positive P3b amplitude, more positive N2 amplitude) relative to the non-contact group.

1.1.2 Hypothesis 2

Football athletes will demonstrate a larger number of errors on Go/No-Go trials compared to non-contact athletes after covarying for head impact metrics (e.g. peak linear and/or rotational acceleration).

1.1.3 Hypothesis 3

Football athletes with higher impact metrics will show increasingly positive error-related negativity (ERN) compared to non-contact athletes. Differences in ERN will become increasingly pronounced as a function of: 1) the severity of impacts incurred over the course of the season and 2) concussion history.

1.1.4 Hypothesis 4

Football athletes will perform similarly to controls on standard clinical measures of neurocognitive function and reaction time after factoring for age and concussion history.

CHAPTER 2

Literature Review

2.1 Concussion

2.1.1 Definition of Concussion

The definition of concussion has evolved over the past decade as research in the field has progressed. The three most widely accepted definitions give a unique perspective and are varying degrees of evidence-based and consensus. Arguably, the most notable of these definitions was provided by the Concussion in Sport Group (CISG) at the International Consensus on Concussion in Berlin where it was defined as "Sport related concussion is a traumatic brain injury induced by biomechanical forces. Four features were listed as useful in clinically defining SRC: caused by an impulsive force to the head or body, rapid onset of signs and symptoms, no abnormalities seen in structural neuroimaging, presentation of a range of clinical symptoms which follow a sequential course.

Alternatively, Carney et al.[31] provided a definition by means of systematic review (i.e. evidence based approach). They concluded that a concussion was "a change in brain function after a force to the head that may be accompanied by temporary loss of consciousness but is identified in awake individuals with the use of measures of neurologic and cognitive dysfunction." Moreover, Carney et al.[32] specifically state that

concussion can be identified with measures of neurologic and cognitive dysfunction. The use of the word "dysfunction" implies a deterioration in function and ignores the possibility for adaptation post-injury and individual differences prior to injury which have been hypothesized in concussed cohorts[33]. Another frequently used definition is provided by the American Academy of Neurology[34] (AAN) who define concussion as a "biomechanically induced alteration of brain function, typically affecting memory and orientation which may involve loss of consciousness." The AAN paper also goes into detail on guidelines of best practice based on four areas of concern: 1) what increases/decreases risk 2) which diagnostic tools are best at identifying post-injury impairments 3) clinical factors and 4) intervention strategies. Of these three supplied definitions the CISG definition is best since it also delineates specific post-injury features.

2.1.2 Concussion Physiology

The physiological alterations produced following a concussion were first presented by Hovda et al.[35] in animal models. In their study they found decreases in chromotome oxidase, a measure of oxidative metabolism, ipsilateral to the site of impact for up to 10 days' post-injury. Changes were most prominent at the level of the cortex and hippocampus. These findings led Giza and Hovda[36] to the theory of the metabolic cascade of concussion which describes the time course of postconcussive pathophysiology. The core ideas from the Hovda et al.[35] study were recently updated in two papers[37,38] which suggest that subsequent to a biomechanical insult there is a deformation of the neuronal membrane causing an efflux of potassium into extracellular space[39]. This disruption to the cell membrane also causes the binding of excitatory neurotransmitters to *N*-Methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This binding in turn increases

neuronal depolarization and the influx of calcium. The adenosine triphosphate (ATP)-dependent sodium-potassium (Na-K) pump attempts to restore the aforementioned changes in cellular physiology. In order to do so it requires an increasing level of energy supplied to the cell via ATP. The high demand for ATP exceeds the cells glucose supply causing an uptake in glucose metabolism. In experimental animal models this process may last anywhere from 30 minutes to 4 hours[40]. In humans, glucose hypometabolism duration seems predicated on the seriousness of the concussive injury with durations of 5 days reported following a concussion but periods of several months following severe traumatic brain injuries[41].

2.1.3 Epidemiology/Incidence - Concussion in High School

Participation in high school sports has seen a steady increase over the past decade[42] to nearly 8 million participants in 2016-17. Based on data provided by the National Federation of State High School Associations over 50% of students participate in some form of athletics. Overall, concussions represent approximately one-tenth of all injuries that occur in high school athletics[43]. Sports-related concussion incidence rates are influenced by several factors including gender, age, sport, and participation level. For example, the most up to date guidelines from the AAN[34] reports a higher incidence rate among all male high school sports (0.61/1000 games) in comparison to collegiate sports (1.26/1000 games). In females, rates of 0.42/1000 games in high school and 0.74/1000 games in collegiate athletics have been reported. Collectively, these reports suggest that as level of competition increases, so does the incidence rate of concussion.

Concussion incidence is periodically defined in terms of "athletic exposures" (AE) which is defined as one athlete participation in a singular sporting event (practice or game). In their analysis of concussion incidence rates in high school and collegiate

sports, Gessel et al.[43] reported that in sports evaluated, concussion rates increased in collegiate sports compared to high school from 0.23 to 0.43/1000 AE. Lincoln et al.[44] reported a steady 15.5% overall annual increase in concussion rate over the course of an 11 year study of 25 high schools. Within high school male athletes, American football (0.60) had the greatest incidence rate followed by lacrosse (0.30) and soccer (0.17). American football had the largest number of participants within this cohort and accounted for nearly half of all concussions within the study, making football an import cohort for investigation[44].

2.2 Repeated subclinical head impacts (RSHI)

2.2.1 Definition of Repeated Subclinical Head Impacts

The terminology used to characterize head impacts that do not result in concussions varies; the most common of which is the term "subconcussion". Other terms used to describe this form of impacts include "subclinical brain damage" and "repetitive subconcussive head impacts"[45]. Others choose to ignore the addition of "subconcussion" and use the term "repeated head impacts". Two recent systematic reviews[46,47] similarly concluded that these terms were poorly defined and ambiguous from study to study. We similarly find these definitions vague[48] and for the remainder of this document will reference these impacts as "repeated subclinical head impacts" (RSHI). We find that the term subclinical more aptly defines these forms of impacts, given that they fail to demonstrate clinical symptoms.

As noted above, concussion is the result of biomechanical forces directly or indirectly to the head which results in clinical symptoms. In contrast, RHSIs are hits below the threshold required to produce clinically observable symptoms[49], yet alterations in brain physiology remain present[50]. At the moment there is a lack of literature

attempting to identify the lower-threshold for RHSIs. However, many have theorized that repeated subclinical head impacts alone or in combination with concussion may lead to long-term health detriments such as CTE[51,52], potentially resulting from the aforementioned changes in brain physiology which are present without acute clinical symptoms that accumulate over time.

2.2.2 Telemetry systems

Associations between neuroimaging data and head impacts have largely relied on self-reported exposure to head impacts, such as "years playing contact sports", to infer the deleterious effect of head impacts on the brain. For the purpose of this discussion we will refer to these studies using the term "head impact exposure". These studies have provided some insight, yet a more direct and objective measure of head impacts is required in order to properly assess the relationship between brain alterations and biomechanical insults.

In recent years, investigators have utilized telemetry systems in order to obtain a measure of head impact frequency and magnitude to corroborate neuroimaging data. These systems allow for a better measure of head impacts compared to "head impact exposure", a categorical variable, which does not as accurately represent head impacts over time. The most popular system at the current time is the Head Impact Telemetry System (HITS, Simbex, Lebanon, NH) which encompasses six single axis accelerometers inserted inside the Riddell football helmets. Although other systems such as the xPatch are also commercially available, they have shown to far greater error rates with some reports suggesting error rates as high as 50% for measures of peak translational and angular accelerations[53]. HITS on the other hand has been previously described with an absolute error between 10% and 20%[54]. For this reason, the discussion that follows will exclude telemetry systems other than HITS.

2.2.3 Incidence/Impact Exposure (HS football) - Impacts per season

In the United States approximately 8 million athletes play in organized sports. Football is the most popular football program with nearly 25% of high school boys participating (over 1 million participants) according to the National Federation of State High School Associations data from 2014-15. Not surprisingly, American football is responsible for over a third of sports-related concussions in team sports[43]. In high school football, athletes sustain an average 652 impacts over the course of a season[55]. However, there is a large variance on the number of hits sustained based on position, with linemen sustaining over double the number of impacts compared receivers, cornerbacks or safeties. Style of play has also been shown to influence the number of impacts incurred over the course of a season with run-first offenses sustaining 50% more impacts than past-first offenses[56].

Kelley et al.[57] demonstrated that athletes with less experience were more likely to obtain their highest magnitude impacts in practice. Whereas athletes with higher levels of experience obtained their larger impacts in competition. Broglio et al.[58] demonstrated that limiting full-contact practices can be an effective measure to reduce the number of impacts sustained over the course of a season by approximately 40%. In summary, several factors have been shown to influence the number of impacts an athlete sustained over the course of a season. Theories have proposed a relationship between the magnitude and frequency of impacts[59,60]. Specifically, it has been it has been suggested that larger magnitude impacts may be less conducive to injury if a larger amount of time is allotted between impacts. Similarly, several smaller magnitude impacts with less time between impacts could prove just as effective at producing an injury. In the following chapter we will evaluate how these impacts can lead to alterations in brain physiology.

2.3 Physiology of Repeated Subclinical Head Impacts

In comparison to concussion there is a limited body of work evaluating the physiology of repeated subclinical head impacts. Several studies have suggested that individuals may show detriments via neuropsychological testing and neuroimaging despite the absence of clinical symptoms[61,62], while others report opposite findings[63–65]. As was the case with early work on concussion, RSHIs has turned to animal models for a basic understanding of the underlying mechanism. Shultz et al.[66] examined changes in neuropathology following RSHIs impacts in Long-Evans rats. In their study, they observed microglial activation and reactive astrogliosis increases at four days' post-injury, both signs of an acute neuroinflammatory response. Evaluating the work by Shultz et al.[66], Bailes[67] suggested that this acute neuroinflammatory response might be consistent with prior work in humans[68]. Thus, potentially providing a mechanism for the neurophysiological sequelae observed following repeated subclinical head impacts. As outlined by Blaylock and Maroon[68], who coined this neuroinflammatory response "immunoexcitotoxicity", this response preferentially effects structures of the frontal lobes, hippocampus and parietal lobes due to their higher sensitivity. These anatomical structures are deeply involved with learning and memory.

Microglia undergo a state of activation and become "primed" following repeated subclinical head impacts. Under normal circumstances microglia are able to switch between phenotypes most notably their phagocytic (reparative) and proinflammatory modes. As outlined above, recurrent impacts cause macrophages to switch into proinflammatory mode (neuroinflammatory response). Consistent trauma, in the form of repeated subclinical head impacts, may render microglia incapable of returning into a reparative mode[68]. This can lead to a hyperactive response from microglia which

then leads to an excess of quolionic acid and glutamate. These excitotoxins lead to the increased presence of hyperphosphorylated tau protein (and neurofibrillary tangles), a hallmark of CTE.

2.4 Neuroimaging

2.4.1 Magnetic Resonance Imaging

Telemetry systems have given researchers a way to quantify impacts during sport and have been paired with imaging techniques with mixed findings. Among the most common neuroimaging methods utilized with telemetry systems is functional magnetic resonance imaging (fMRI). Derived from MRI techniques two forms of diffusion weighted imaging have been recently applied to the study of traumatic brain injuries: diffusion tensor imaging (DTI) and diffusional kurtosis imaging (DKI). Both DTI and DKI are based on water's diffusion rate within tissues.

Diffusional kurtosis imaging (DKI) is an extension of MRI. In the simplest of definitions DKI evaluates the probability of water diffusion based on a non-Gaussian function. Diffusion tensor imaging (DTI) is primarily utilized to observe white matter changes in living humans[69], which is of particular interest when it comes to concussion.

Thus, the neurophysiological theories of RSHI may help corroborate findings observed by Bazarian et al.[70] who showed deficits in working memory in humans. In their study, a single football season without clinical concussion resulted in working memory changes in athletes which correlated with multiple head impacts as measured using telemetry systems. Athletes showed increases in both functional anisotropy (FA) and mean diffusivity (MD), which persisted after 6 months of non-contact rest. This aligns

with prior work which also observed no association between head impact data and neuropsychological measures[71].

A functional magnetic resonance imaging (fMRI) study by Breedlove et al.[72] observed blood-oxygen-level dependent contrast imaging (BOLD) changes in an asymptomatic group of teenage football athletes despite a lack of clinical impairment. Moreover, they found that within their concussed group, changes in fMRI measures were more highly correlated to the hits experienced than the presence of concussion. Within the same sample Talavage et al.[73] noted that half of their non-concussed players showed decreases in activation within the dorsolateral prefrontal cortex (DLPFC) and cerebellum during a working memory task. Curiously, these players had a higher number of hits over the course of the season compared to other players on the same team, but in other positions (e.g. quarterbacks, receivers etc.). These results suggests that changes in neuroimaging may be associated with repetitive subclinical head impacts. However the evidence of repeated subclinical head impacts' effect on neuropsychological test performance is mixed with subclinical head trauma shown to impact neuropsychological test performance on domains of working memory, impulse control and visuomotor speed[74]. While others report little to no findings[55,65].

Johnson et al.[75] showed changes in the default mode network in rugby players 24 hours post-game. In this study, athletes showed increased connectivity from the left supramarginal gyrus to bilateral orbitofrontal cortex and decreased connectivity from the retrosplenial cortex and dorsal posterior cingulate cortex. The researchers also investigated whether athletes with a concussion history showed any differences in functional connectivity following repeated subclinical head impacts. Indeed, they found that individuals with a concussion history showed decreases in functional connectivity following repeated head impacts, whereas athletes without a concussion history showed the opposite effect. This finding may help corroborate theories that repetitive

head impacts can lead to chronic changes in cellular metabolism[67].

Bahrami et al.[76] utilized HITS to accompany their diffusion tensor imaging (DTI) study evaluating changes in white matter integrity over the course of a youth football season, documenting a significant relationship between fractional anisotropy (FA) changes and head impact measures. An evaluation of their regression model raises questions about the data used to render this conclusion as an outlier is possibly driving the effect. The authors failed to comment on the strength of the relationship if the outlier was removed and/or provide further details on the cause of this suspect data point. Nevertheless, this was among the first evaluations of the relationship between repeated subclinical head impacts on white matter integrity. It should also be noted that HITS data was solely used to compute a cumulative exposure measure known as combined-probability risk-weighted cumulative exposure (RWECP). This measure was used despite prior research identifying that cumulative measures failed to identify changes in this particular cohort[55]. Despite previous findings, a cumulative metric may one day elucidate how changes over the course of a season predict concussion. For this reason more current measures such as Impact Density may be preferable to identify risk exposure measures[77].

DKI has also been shown to be sensitive to repeated subclinical head impacts[62]. Davenport et al.[10] reported the number of total impacts incurred over the course of season showed a significant association with only one DKI measure, axial and radial extra-axonal diffusivity decreases in white matter areas. However, the authors also implemented a risk weighted cumulative exposure combined probability (RWECP) a measure which summed the peak linear and rotational impacts as a function of the number of impacts[78]. RWECP showed several associations with DKI-derived data suggesting that number of impacts alone is not responsible for alterations in white matter over the course of a season. Similarly, the authors reported that risk

weighted exposure using linear or rotational acceleration explained variance in much fewer DKI metrics than RWECP. These results suggest that both number of impacts and the magnitude of impacts must be taken into consideration when predicting brain alterations caused by impacts.

Based on the relatively weak association between impact metrics derived from HITS data, Merchant-Borna et al.[79] incorporated the time between hits (TBH) which is theorized to have an inverse relationship with brain alterations. By weighing the time between hits with common head injury metrics (Gadd severity index (GSI), head injury criterion (HIC15), Head Impact Technology severity profile (HITsp)) they were able to explain up to 77% of the changes in white matter. Among their findings were decreases in fractional anisotropy (FA) over the course of the season.

FA is theorized to measure fiber density and axon diameter although its use has a marker of white matter integrity been debated[80]. The association between cognitive tests and DTI measures has been mixed with some studies failing to demonstrate any correlation[81]. Additionally, although many propose that decreases in FA are a sign of decreased white matter integrity, some studies have shown that increases in FA are associated with poorer visuospatial abilities[82]. Ergo, it may be imprudent to generalize conclusions on increases or decreases in FA based on the entire brain given that the benefit may change as a function of neuroanatomical location.

Despite possible misinterpretations that may occur with this form of data and inconsistent gender differences reported[45], biomechanical insults have been shown to produce DTI-related related changes in football[62,76,83,84], boxing[85,86], soccer[87,88], ice hockey[45,84,89], soccer[90], wrestling[91], rugby[92], martial arts[93] many of which occur without clinically detectable changes or diagnosis of concussion. Changes have also been observed in asymptomatic athletes[94,95]. The significance of these findings and their clinical applicability remains questionable at the current time. Moreover,

fMRI has a higher cost, less temporal resolution and is impossible to administer on the field in comparison to other neuroimaging methods such as electroencephalography (EEG).

2.4.2 Electroencephalography (EEG)

2.4.3 EEG Background

EEG was the first neurodiagnostic method to demonstrate alterations in brain function following a concussion as early as the 1940s[96–99]. The quantitative electroencephalograph (qEEG) is a technology that allows the digitization of brain signals so that they can be analyzed mathematically. Strip-chart (paper) electroencephalography (EEG) as well as older studies prior to the development of qEEG relied on visually inspecting each record. Many studies[100–102] have questioned the reliability of visual examination given its high level of subjective interpretation. Consequently, research in this field has switched focus to quantitative measures. EEG can also help elucidate white matter changes as white matter architecture correlates highly with EEG alpha rhythm[103,104] . Although it should be noted that this white matter index is much less sophisticated than those previously described in DTI.

Among the most common procedures to perform on electroencephalographic data is Fast Fourier Transformation (FFT) which results in the raw signal being divided into user-defined frequencies. These frequencies are organized from slowest to fastest and are usually denoted as delta, theta, alpha, beta and gamma. The resulting graph from these spectra is referred to as the power spectrum. Although the specific criteria for each of these bands can vary slightly between works, in general the delta band is characterized by 0.5 to 4 Hz, theta from 4 to 7 Hz, alpha from 7 to 13 Hz, beta from 13 to 39 Hz and finally gamma is characterized by any frequency of 40 Hz and

above. Prior studies suggests that there are two separate (independent) alpha bands which are commonly referred to as either alpha1 and alpha2 or lower and upper alpha frequencies[105–109]. Beta on the other hand is divided into three frequencies, although some studies use either two or one. Power spectral density, more commonly known as EEG power, calculates variations in energy as a function of frequency. Coherence, a measure of the degree of similarity between sensors[110] can also be computed with measures ranging from 0 (low coherence) to 1 (high coherence).

2.4.4 EEG and Concussion

Several studies have shown neurophysiological alterations following concussion utilizing electroencephalography, however findings are often inconsistent due to differences in experimental methodology, concussion criteria and time post-injury. Among the most consistent findings are increases in slow-wave activity in concussed subjects relative to controls[78,111–113]. This characteristic was reported in many early EEG studies[97] where it was believed to be a measure of brain damage. Others have also reported decreases in alpha activity[114]. Findings in severe TBI have been much more consistent that those in mTBI. Nevertheless, studies have repeatedly shown that clinically asymptomatic individuals still show disruptions in brain activity as measured by qEEG[115]. Concussed individuals have also been shown to exhibit significantly less delta activity than controls while standing[116] which may help corroborate movement dysfunctions seen within this cohort[117,118].

More recent studies have utilized advanced metrics to evaluate changes. Teel et al.[115] found significant decreases in EEG power and increases in coherence in participants who had a concussion history in the previous year. EEG alterations have also been repeatedly observed despite subjects returning to baseline by clinical guidelines[119]. EEG has also been shown to discriminate between multiple concus-

sive injuries, whereby composite EEG measures took longer to recover in athletes following a secondary mTBI in comparison to athletes who had sustained their first mTBI[119,120].

Animal studies have provided some insight into the relationship between qEEG measures, repeated head impacts, biomarkers. Most notably, Mountney et al.[121] who collected qEEG analyses at 12 hours, 1, 2, 3 and 14 days post-injury demonstrated bilateral slowing acutely and transiently. The significant increase within the delta band was responsible for a decrease in all power frequencies, particularly the theta band (5-8 Hz). This effect eventually subsided as delta levels between groups were indifferent by 7 days' post-injury. Comparisons were also made between rats who had sustained a single impact and those with repeated impacts. They found that rats who had sustained repetitive impacts had significant increases in biomarkers within the hippocampus and a 20-fold increases in proteins indicative of CTE compared to controls. The applicability of these results to humans as yet to be properly elucidated.

2.4.5 Repeated Subclinical Head Impacts EEG findings

Repeated subclinical head impact EEG findings also suffer from the methodological inconsistencies of EEG concussion studies. This point of view was seconded by Tarnutzer et al.[122] who concluded that the two studies[123,124] which evaluated the effect of heading in soccer were of low quality and given the limitations, conclusions from these studies were "unconvincing". Earlier work utilizing non-quantitative EEG showed some promise. Haglund and Persson[125] observed increased EEG abnormalities in boxers in comparison to athletes in sports with lesser degrees of repeated head impacts (soccer and track and field). Approximately 32% of boxers had abnormal EEG deviations in comparison to 16% in soccer and 10% in track and field athletes.

2.4.6 Event-Related Potentials (ERP)

2.4.7 ERP Background

Event-related potentials are phase locked potentials occurring endogenously in the brain[126] related to external events. By evaluating the brain's response to external events, researchers are able to investigate specific electrophysiological responses related to cognitive processes ranging from vision, motor control and executive function amongst others. While investigating these hypotheses several protocols have become standard, among them are the Go/No Go and Oddball Task.

During the oddball paradigm two different types of stimuli are presented to the participant. The first is frequently occurring (termed the "standard" stimulus) and the second is less frequently occurring (termed the "oddball" stimulus). Stimuli are presented every 1 to 2 seconds. The oddball paradigm can present stimuli visually or using sound. During the Go/No Go task participants are presented with stimuli some of which require a response (Go condition) while others require the participant to suppress a response (No Go condition). This particular paradigm has been shown to be particularly effective when assessing frontal inhibition.

The event-related potentials that result can differ according to which paradigm is used, hence we will restrict our discussion to those related to the visual Go/No Go and Auditory Oddball paradigms. ERP measures are denoted starting with the letter "N" if they are negative or the letter "P" if they are positive. The second part of the notation refers to roughly to the peak latency of the component following stimuli presentation. For example, P1 (also known as P100) refers to a positive wave which occurs 100ms following stimulus presentation. P1 has been associated with automatic attention to salient stimuli. Other common positive potentials include the P3 which is associated with stimulus evaluation. The P3 is often separated into two

subcomponents the P3a and P3b. The P3a, also known as the novelty P3[127], has a frontal scalp distribution which peaks around 250 to 280 ms and is associated with attention engagement. The P3b is seen best along central and parietal electrodes and is larger for uncommon stimuli and relies on task-defined probability. Finally, the N1 has been associated with low-level visual features and the N2 with automatic attention allocation. Many of these ERP components will show distinctly different presentations based on the modality they are presented. For example, the P1 wave in auditory task is distinct from the P1 wave in visual tasks.

2.4.8 Event-Related Potentials and Concussion

ERP investigations on concussion have mostly focused on long-term effects. With very few studies evaluating acute injury. The most widely reported findings are that individuals with a concussion history show decreases in P3 amplitudes relative to controls[128–133], they also less consistently showed longer P3 latency[134–137]. For example, Broglio et al.[49] found significant decreases in P3b and N2 amplitudes 3.4 years post-injury. They attributed group differences in N2 to "a less effective response inhibition process under more intense decision making". Dupuis et al. also found decreases in amplitude in the P300 wave in symptomatic concussed individuals[130]. Their findings were isolated specifically to frontal and central regions.

P3 word latency has also been shown to significantly increase as a function of a player's number of concussions. With athletes in the 3+ concussion group showing latency increases of approximately 45 ms[135]. Roche et al.[101] found a significant association between reaction time, alpha power and Go-trial reaction time. Where decreases in alpha power were associated with longer reaction times.

In summation, consistent findings have been shown in those with a concussion history in P3b. Additional research is needed to clarify conflicting reports on other cognitive

measures such as the P3a. Researchers should also be cautious when generalizing results from one ERP study to the next when different paradigms are utilized. Additionally, it should be noted that although a plethora of ERP research on those with a concussion history, there is minimal work accessing athletes acutely (i.e. within the first week post-injury).

Despite these findings, there is a significant gap in literature on the potential effects of repeated subclinical head impacts on event-related potentials. In fact, at the time of writing this document there is yet to be an investigation on the relationship between these variables. Given the potential of ERPs to unearth findings, further research utilizing ERP may elucidate repeated subclinical clinical head impacts phenomena that have yet to be described in the literature.

2.4.9 Error-related Negativity

2.4.10 ERN Background

Error-related negativity is phase-locked stimulus-response that is measured using event-related potentials (ERP). Specifically, researchers noted a difference in ERP waveforms between correct and incorrect response trials. The ERN is seen when contrasting error trials vs correct trials. In error trials there is a distinct negative onset in the ERP activity which peaks at approximately 100ms. The amplitude of the ERN is greatest along the midline frontal and central electrodes[138,139]

Early models claimed that the anterior cingulate area, more specifically its dorsal region was the source of ERN generation. However, a more recent study by Hochman, Orr, Gehring[140] suggest that the medial prefrontal cortex may act as the sole source of the ERN (pre-supplementary motor area). Studies in subjects with sickle cell disease[141], which targets the lateral prefrontal cortex, have shown that this area of

the cortex plays a primary role in the generation of the ERN as subjects with lesions in this area show an abolition of the ERN. Below is a synopsis of the four most common theories used to describe the ERN: error detection, conflict monitoring, reinforcement learning and affect/motivation.

2.4.10.1 Error Detection Theory

Error-detection theory of the ERN proposes that the ERN reflects the process of comparing the output of the motor system with the best estimate of a correct response at the time the ERN occurs[139]. Moreover, the close proximity of the ERN to the stimulus suggest that the ERN is either 1) a result of the comparison between these processes or 2) the result of the process itself.

2.4.10.2 Conflict Monitoring

Conflict monitoring does not provide a neuroanatomical area responsible for its processing. Rather it claims that the ERN can be explained by response conflict. Such that when more than one response is available for a given stimulus the system tracks performance and uses this response in subsequent trials. Proponents of this theory have shown that the ERN can be elicited by response conflict[142]. Moreover proponents of the conflict monitoring theory, claim that the error-detection theory is computationally implausible. Since it requires that a comparator contain the incoming response as well as a representation of the correct response. If the brain already contains the correct response, then why not simply execute it? This theory has recently been brought into question in a 2014 paper by Hochman, Orr and Gehring[140].

2.4.10.3 Reinforcement Learning

The reinforcement-learning theory of the ERN proposes that the basal ganglia creates a signal when something is more wrong than anticipated[143]. There are inherent assumptions to this model which includes that it must respond to the earliest form of information since there is no association between stimulus-response and its reward. Once reward values have been associated with the appropriate stimulus-response, subsequent trials should occur at a faster rate.

2.4.10.4 Affect and Motivation

This theory does not directly contradict any of the aforementioned theories. It does however place a special emphasis on the role of the limbic system in the processing of errors[144]. This theory claims that the potency of errors on part of the subject are responsible for the ERN.

2.4.11 ERN Theories as it Pertains to Concussion

Each of the aforementioned ERN theories has an implied underlying mechanism. Baker and Good[145] have shown that individuals with a history of mild traumatic brain injury (mTBI) show less aversion to negative stimuli. Although the authors believed this was due to differences in activation in the Ventral Medial Prefrontal Cortex (VMPFC) it is possible that findings provided by Althaus et al.[146] might be applicable. Specifically, Althaus et al.[146] found that individuals with the short allele of a serotonin receptor gene processed negative stimuli more intensely. They also showed greater habituation to negative stimuli, most likely due to increased value of the response. This may also align with prior animal research where ventral basal thalamic neurons demonstrated atrophy 28 days post-injury[147]. To date, no work has

yet to associate anxious personality traits with mBTI (which is also a predisposition of the short allele) these results provide insight into an alternative mechanism. Baker and Good's findings[145] may support the use of the Affect/Motivation theory in the evaluation of the ERN in those with a concussion history. It should be noted that the limbic system (affect/motivation) changes in concussion have been poorly evaluated.

DeBeaumont and colleagues[134] found a longer latency of the P3a in their concussed cohort. This would suggest that individuals with a concussion history demonstrate increased difficulty processing novel stimuli in comparison to controls. Based on the Reinforcement Learning theory this would lead to an irregular signal via the basal ganglia, subsequently producing changes in the ERN between groups.

Error-detection theory may also find support from prior research demonstrating errors at the level of the motor system in those with a concussion. For example, DeBeaumont et al.[134] suggest failed motor learning is present which may account for findings by Lynall et al.[148] who found that NCAA athletes who received a concussion were twice as likely to receive a subsequent lower-body injury in comparison to controls. The mechanism for this rather strange association was theorized in a previous paper[117], in that the cerebellum acting as the comparator of the execution of movement inappropriately mediates incoming/outgoing feedback from prior responses. Which leads to an increase risk in the motor patterns[118] despite a more conservative gait strategy. Several other researchers have shown motor deficiencies persists several years post-injury in comparison to clinical symptoms (which are usually evaluated by neuropsychological tests)[117,118,149].

In terms of conflict-monitoring one could theorize, based on findings by Eckner[150] showing increased reaction time in concussion, that individuals with a concussion will take longer to process high conflict trials in compared to controls. Additionally, if the ERN represents the motor output (and not the comparator of responses) then

we would expect to see a smaller decrease in trials that are more congruent/similar. Curiously, proponents of this theory have yet to demonstrate how varying levels of congruency between competing responses affect the ERN.

2.4.12 ERN and Concussion

Prior ERP research has observed significant differences in individuals with traumatic brain injuries specifically along fronto-central sensors. In their study, Dupuis et al.[130] attribute this finding to the assumption that most head impacts occurred at the front of the head. However, an alternative explanation might be at odds. The assumption that most impacts occur at the front of the head is flawed. A study of 319 NCAA athletes from six universities observed that front impacts account for approximately 50% of concussive injuries[151] Moreover, differences have been shown based on position of play[152]. Finally, Liao et al.[153] observed that concussed NCAA football athletes had a higher percentage of impacts on the sides and top of the head in comparison to their non-concussed colleagues[58].

Moreover, it is plausible to consider that these detriments are not due to the location of the impacts but rather due to neuroanatomical deficits localized along this region. This area of the brain, home to the DLPFC and ACC, shows decreased grey matter volume in concussed individuals[154,155]. The ERN, which involves specifically the frontocentral region, is well positioned to evaluate this hypothesis. Few studies have evaluated changes in the ERN in concussed cohorts but those who have, demonstrated significant findings. Pontifex et al.[156] showed no differences in correct trials but observed decreases in ERN amplitude at FCz in error trials. In accordance with prior literature, they observed larger post-error positivity (Pe) amplitude on error trials, but there were no differences between concussed and control groups on this metric. These findings were replicated by Larson et al.[157] on a Stroop task in individuals

with severe TBI. They also found a very strong correlation (r=-0.325) between the ERN amplitude and previous number of mTBIs. Follow-up studies by Larson et al.[158] in those with severe TBI indicate that variations in ERN are not associated with injury severity or time post-injury.

2.5 Long-term Effects of Concussion

2.5.1 Chronic Traumatic Encephalopathy (CTE)

CTE has been described by atrophy of widespread areas of the brain preferentially effecting areas surrounding sulci and near ventricular and vascular areas[159]. It also is accompanied by reductions in brain weight and enlargement of the ventricles[160]. McKee et al.[159] indicated that symptoms included indicated "increased impulsivity, aggression and suicidality". The cause of CTE has been attributed to repeated head impacts, which include concussion[52,159].

Given its proximity to the suicide of famous athletes at the time, the link between CTE and suicide warranted a review. The National Institute for Occupational Safety and Health (NIOSHA)[161] and Rao et al.[162] both demonstrated that there was no "suicide epidemic" in athletes. NIOSHA showed that NFL players decreased rate of death was 46.4% less than the general population whereas Roa et al showed that suicide accounted for under 8% of the mortality rate in NCAA athletes. Both these figures are lower than observed in the normal population. Wortzel and colleagues[163] concluded that the link between CTE and suicide was "speculative at best" and further noted that many of the publications on the topic of CTE were either case control studies and or had subjects which were used in previous studies. In total, the cause of death from 5 of 21 athletes in the CTE bank were due to suicide. Additionally, Wortzel stresses that the lack of proper controls was concerning. Iverson

and colleagues[164] discussion paralleled that of Wortzel emphasizing that the lack of prospective, epidemiological studies warranted researchers in the area to remain conservative in their conclusion as not to falsely alarm the public. Gardner[165] once again affirmed this stance but identified in greater detail some of the methodological issues concerning recent "findings" on CTE. Among them were selection bias, recall bias, reverse-causation (for example see Lee et al., 2012) and cohort dependency.

Other research is conflicted. Lehman et al.[166] showed that NFL athletes were three times more likely to die from a neurodegenerative disease compared to the normal American population. The study also concluded that speed positions were at higher risk than non-speed positions. In a sample of high school football athletes from the 1940s and 1950s Savica et al.[167] found no increase in any neurodegenerative disorders. Hazrati et al.[168], in a study of retired Canadian Football League athletes, showed that despite their large exposure to contact some of the athletes had no signs of CTE.

Early work by Mendez[169] reviewed neuropsychiatric studies in boxers and theorized that repeated blows to the head were closely related to CTE. More recently research has shown in animal models that repetitive hits is responsible for CTE rather than a history of concussion[52]. Given this recent finding, more research is needed evaluating subclinical impacts and their neurophysiological impact.

Groundbreaking work completed by the National Institute of Health[170] may have illuminated evidence to explain the link between CTE and repeated subclinical head impacts. In their work they utilized a form of MRI known as FLAIR (fluid attenuated inversion recovery) which nulls the signal from fluids (e.g. cerebrospinal fluid (CSF)). In doing so, areas such as the meninges and periventricular areas can be observed. Earlier work by this group had shown that nearly half of patients with minor head injury had meningeal vascular damage[171]. In this study they hoped to examine the recovery rate of the meninges post-injury. Of the 209 patients studied 104 showed

meningeal vascular damage within 2 days following a mild traumatic brain injury (mTBI). Within these 104 patients who showed meningeal vascular damage, 83% showed resolution approximately 18.9 days later.

In order to investigate the findings in a more controlled environment, this research group performed a follow-up study to investigate meningeal damage recovery time caused by mild traumatic brain injury (mTBI) in mice. Using intravital two-photon microscopy (TPM), and an injection of markers used specifically for vascular leakage, they were able to observe severe "vascular leakage" post-injury which ceased approximately one-week later. At four days post-injury, damaged blood vessels were repaired, which although could be distinguished visually from uninjured vessels, showed no differences in blood flow. Finally, at approximately seven days post-injury revascularization of the meninges was complete. These results clearly demonstrate that recovery following impacts follows a strict temporal regulated system.

Finally, within the same study Russo et al.[170] wanted to examine the effect of impacts subsequent to the initial injury would affect the aforementioned recovery process. This methodology would more appropriately describe the environment athletes are exposed to due during sports. They found that a secondary injury within 24 hours following the first injury disrupted the revascularization process. Secondary injuries which occurred four days following the initial injury had no such effect. This suggest that the timing of the second impact, assuming it exceeds the unknown threshold, could delay the re-vascularization of the meninges. These results parallel discussions from telemetry research which has eluded to a tradeoff between the magnitude of a RSHI and the time between them. Over time, it has been suggested that vascular leakage promotes cellular death[172], a hallmark of CTE.

2.6 Conclusion

There has been a growing trend in recent literature demonstrating the potential detrimental effects of repeated subclinical head impacts on brain health. These studies contain several possible confounds that may offer alternative explanations to the findings presented. Furthermore, many of these studies are prone to selection bias, where control groups are often absent in the experimental design[173]. Prior studies correlating biomechanical impacts to detriments in brain function have also used self-reported measures of impact exposure[174]. Studies with more specific measures of repeated subclinical head impacts (i.e. using telemetry systems) may help clarify the link between these two measures. Furthermore, it should be noted that most studies evaluate the professional ranks despite the fact that younger athletes make up the largest cohort of active individuals.

There are over 7.5 million high school students participating in athletics each year, which dwarfs the numbers at the collegiate and professional levels. Within this study we will have direct measures of both brain activity and repeated subclinical head impacts over the course of an entire football season. This study will fill a significant gap in the current literature which has failed to evaluate the effect of RSHIs and electrophysiology. Moreover, we aim to investigate this relationship within vastly understudied cohort of adolescent athletes.

The goal of the following investigation is to fill gaps in the existing literature on how repeated subclinical head impacts over the course of a season in adolescent football athletes can cause acute changes in brain activity. These changes will be compared to an age matched non-contact athlete group. The data may help provide insight into the strength of the relationship between impacts to the head and detrimental changes in brain health which has been alluded to in prior work in the field. Finally, this work may help provide a foundation for rehabilitative care should changes be noted.

CHAPTER 3

Methods

This study is a retrospective investigation of prior data[175]. A synopsis of the testing protocol used in the study is described below.

3.1 Testing Protocol

Participants underwent testing at three different time points during the 2013 to 2015 fall (September to November) academic sports season. The first measurement was prior to the start of the season. The second was during the season and the final measurement was completed at the end of season. All athletes completed where a detailed questionnaire (Appendix **??**) at baseline.

Participants were excluded from the study if they had known neurological disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), learning disabilities, concussion or traumatic brain injury (TBI) in the previous 6 months. Participants were also excluded from this study if they had a history of skull fractures, brain bleeds or any other underlying brain condition.

3.2 Participants

A total of 24 participants were recruited and informed assent and consent were obtained. Twelve high school football athletes served as the "contact sport exposed" group. The "non-contact" group was composed of athletes who participated in non-contact sports which included golf, track and basketball amongst other. This group of athletes had no reported exposure to contact sports throughout the study period. Age in years during preseason measurements was $M = 16.52$, $SD = 0.72$ years for football athletes and $M = 17.01$, $SD = 1.14$ years for non-contact athletes. Height of the football athletes and non-contact athletes was $M = 179.28$, $SD = 6.45$cm and $M = 176.74$, $SD = 9.27$cm respectively. Finally, the mean weight of football athletes was $M = 81.25$, $SD = 13.65$kg and $M = 71.48$, $SD = 10.86$kg for non-contact athletes.

3.3 Instrumentation

3.4 Health Related Quality of Life

Health-related quality of life measures included the Health Behavior Inventory (HBI), Satisfaction with Life Scale (SWLS) and symptom inventory. HBI and SWLS scores were summed into their respective components (Cognitive and Somatic items in the HBI).

3.4.1 Satisfaction with Life Scale (SWLS)

The Satisfaction with Life Scale is a 5-item survey utilizing a 7-point Likert scale that ranges from 1 "strongly disagree" to 7 "strongly agree". Values from each item

are added to obtain one aggregated score. The SWLS has been shown to represent a subject's satisfaction with life as a whole[176].

3.4.2 Health Behavior Inventory (HBI)

The Health Behavior Inventory (HBI) is a 20-item survey utilizing a 4-point Likert scale that ranges from "never" to "often". It has two components: 1) a Cognitive item list and 2) Somatic item list. Higher scores reflect lower participant perceptions of Health-Related Quality of Life[177,178].

3.4.3 Demographics

Pre-season testing included a demographics questionnaire which contained FITBIR TBI Common Data Elements (e.g. age, height, weight) as well as other variables of interest (e.g. medications, caffeine use, sleep, family history of migraines). Participants were also questioned on their history of neurological disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), learning disabilities, concussion or traumatic brain injury (TBI). Football athletes had significantly more concussions (composed of both diagnosed and undiagnosed) $M = 0.75$ [0.25, 1.25] vs. $M = 0.17$ [0.00, 0.42], $t(15.3) = 2.13$, $p = .050$. However, the effect was almost exclusively driven by differences in the number of diagnosed concussions, where football players had a significantly higher number in comparison to their non-contact counterparts $M = 0.67$ [0.17, 1.17] vs. $M = 0.00$ [0.00, 0.00], $t(11.0) = 2.60$, $p = .025$.

3.4.4 HITS

Football athletes were equipped with helmets containing the Head Impact Telemetry System which recorded impacts during all practices and games throughout the

entire season. The system recorded both the location and magnitude of each impact internally. Each encoder is composed of six single-axis accelerometers measuring at 1 kHz. If data from one accelerometer exceeds 14.4g, data 8 milliseconds before the 14.4g threshold and 32 milliseconds after, are stored internally. Aberrant impacts (e.g. athlete throwing his helmet on the ground) were noted in a research diary and removed prior to subsequent analyses. Data with linear accelerations under 10g were also filtered.

3.4.5 Event-Related Potentials (ERP)

Electrophysiological measurements were also taken where athletes completed an Auditory Oddball and Go/No-Go task before the start, during and after each season. The subject of this investigation is to analyze Go/No-Go data, Auditory Oddball results will be analyzed elsewhere. Data were collected in accordance to the procedure outlines in the Geodesic Sensor Net Technical Manual[179]. Measures of head circumference were taken and each participant was fitted with an appropriately sized cap. International 10/20 system locations were deduced using Luu and Ferree[179]. For reference, Figure 3.1 below demonstrates the EGI electrode number and the approximate 10/20 location, the electrode locations are highlighted in red.

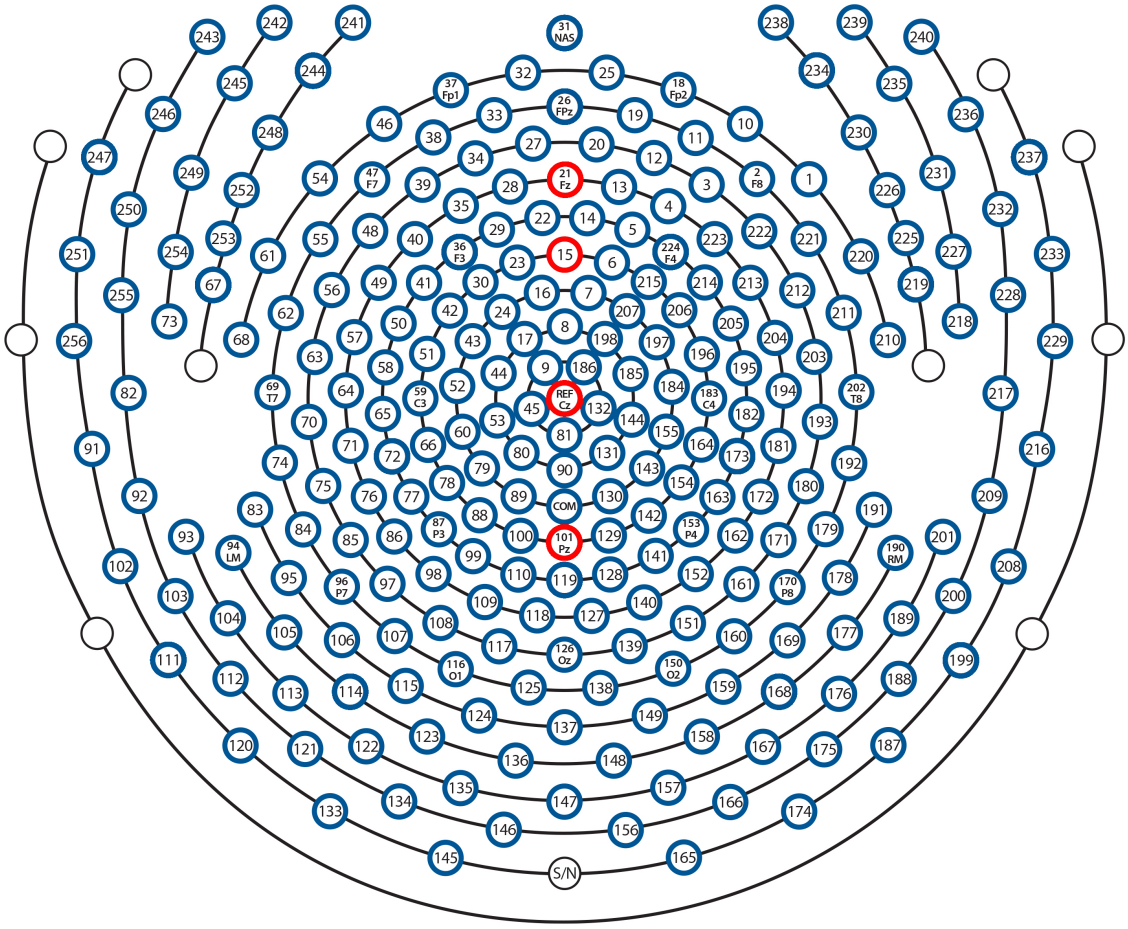

Figure 3.1: EGI 10/20 Electrode Position

Raw data were imported into EEGLAB and subsequently filtered with a 1.5 Hz low pass and 40 Hz high pass filter. Bad channels were rejected using built-in tools and later interpolated. Once completed, data were referenced to the average electrode reference.

Event-related potentials, derived from electroencephalography, are phase locked potentials occurring endogenously in the brain[126] related to external events. External events generally consists of either a stimulus being presented to the participant (e.g. N2, P3) or the participant's response to the stimulus (e.g. ERN < Pe). Epochs were analyzed to confirm the absence of overlap between conditions. There was a

total of four conditions within the Go/No-Go task (Table 3.1 below).

Table 3.1: ERP Trial Type Abbreviations

Trial Type	Abbreviation
Correct/Go	GoC
Incorrect/Go	GoI
Correct/No-Go	NgC
Incorrect/No-Go	NgI

CHAPTER 4

Project 1: The Association Between Head Impact Metrics, Contact Sports and Stimulus-locked Electrophysiological Indices of Brain Function

4.1 Abstract

In recent years, there has been an increasing amount of literature demonstrating neurophysiological changes associated with concussion history and contact-sport exposure. Few studies have incorporated baseline measures in addition to athletes with variable levels of concussion history and contact sport participation to evaluate these changes. Ergo pre-existing group differences, other than the level of contact in sport, may explain these findings. Accordingly, the principal objective of this study is to investigate changes that occur over the course of one season of play in both contact (football) and non-contact athletes while accounting for pre-existing concussive injuries. **Methods:** Twenty-four high school athletes (Age $M = 16.77$, $SD = 0.96$years) participating in football (n=12) and non-contact (n=12) sports completed a Go/No-Go task at three time points: before the start of the season, during the season and at the end of season. Stimulus-locked event-related potential components (i.e. N2, P3b)

were subsequently calculated. Concussion history for each athlete was also collected at the start of the season. **Results:** Changes in N2 amplitude were observed as a function of both athlete type and concussion history. Contact-sport athletes with a concussion history demonstrated reductions in these cognitive indices, while non-contact athletes with a concussion history demonstrated an increase relative to their non-concussed peers. Analyses of telemetry data in contact-sport athletes revealed decreases from baseline in P3b and N2 amplitude were compounded by concussion history once a threshold in linear and rotational impact density was exceeded.
Conclusion: Together these findings suggest contact-sport participation, in athletes with a concussion history, show greater detriments in neurophysiological indices associated with cognitive control, information processing and executive function. Results from this study provide a timely and necessary study of head impact metric thresholds required to produce detrimental changes in brain function as measured via electrophysiology as measured in differing levels of contact-sport participation.

4.2 Introduction

Concussion is a prevalent injury among athletes induced by biomechanical forces[2] occurring at a rate of 1.6 to 3.8 million annually in the USA[1]. The increase in awareness within the general public and fear of long-term detriments has led several high profile football players to retire in their prime[180–182].

Despite a general consensus that the majority of clinical symptoms resolve within 14 days post-injury as measured via standard neuropsychological testing[183,184], increasingly reports using more sophisticated measurements of cognitive function demonstrate alterations in function within asymptomatic athletes long after clinical recovery[185–187]. The need for a more sophisticated measures of cognitive function

following concussion is required to investigate recovery within these athletes.

In a systematic review performed by Manley et al.[188], concussion was reported as a significant risk factor to decreases in long-term neurocognitive function[188]. Yet, recent work[8,189] on a neurocognitive disorder (i.e. chronic traumatic encephalopathy (CTE)) has highlighted the importance of subclinical head impacts in addition to concussion.

Animal work has investigated the cellular processes that occur following both concussive and subclinical head impacts. In general, a neuroinflammatory response is observed following an impact. This is induced by the increased presence of microglia which release cytokines and excitotoxic amino acids. Under normal circumstances, microglia are able to switch between phenotypes most notably their phagocytic (reparative) and proinflammatory mode (neuroinflammatory response)[190,191].

Shultz et al. conducted a series of studies[191–193] comparing the cellular response during concussive and subclinical head impacts. They noted that although the subconcussive rat group failed to show behavioral impairments observed in concussed rats after a single impact, they did show a similar neuroinflammatory response to the concussed group of rats. Their results also parallel those of other animal models using larger impacts[194] such that rats given shorter recovery times between impacts showed significant increases in microglia and macrophages at 4 days post-injury compared to rats who were given additional time to recover (4 weeks).

The morphological changes of microglia are not unique to head impacts but has also been observed in neurological diseases such as Alzheimer's[195], multiple sclerosis[196–198], Parkinson's[199] and general aging[200]. It has been theorized that the presence of these diseases render microglia incapable of returning into reparative mode[201]. In more severe forms of brain injury, the microglial activation process in humans has been shown to remain present up to 17 years post-injury[202]. This

activation can lead to a hyperactive response from microglia which then leads to an excess of quinolinic acid and glutamate. These excitotoxins lead to the increased presence of hyperphosphorylated tau protein (and neurofibrillary tangles), a hallmark of CTE.

The use of *in vivo* neuroimaging methods to evaluate cellular level changes in the brain due to impacts, as used in the aforementioned animal studies, have yet to be developed for humans. Consequently, other forms of neuroimaging, such as event-related potentials (ERP), must be utilized to investigate the relationship between brain alterations as a function of concussion and head impacts. ERP components have been associated with a variety of cognitive functions such as error processing (ERN)[16] and awareness (Pe)[17,18], response inhibition (N2, P3)[25,26,203], attention (N2)[204] and perception[205] among others. Increases in P3b amplitude have been associated with increases with learning[19–21], in acheived task proficiency[22] as well as exercise[23,24]. These indices of brain function have also been examined following subclinical head impacts.

Moore and colleagues[206] evaluated ERP changes in three groups: non-contact and contact athletes with no concussion history and a third group composed of contact athletes with concussion history. They observed reductions in P3a and P3b amplitude in both contact athlete groups. Within their study contact athletes without a concussion history were used as a proxy to investigate the effects of subclinical head impacts. They observed reductions in P3a and P3b amplitude in both contact athlete groups. Reductions in N1 amplitude were only observed in contact athletes with a concussion history. The study concluded that alterations in contact athletes without a concussion history, although detrimental, were less than contact athletes with a concussion history. Among the limitations present within the study were the absence of non-contact athletes with a concussion history. The results from this study imply

that a unique relationship exists between subclinical impacts and concussion history.

The goal of the present study therefore, is to further investigate this relationship while using a more direct, rather than self-reported, measure of repeated subclinical head impacts. In accordance with prior work, increases in P3b amplitude and/or shorter latency will be interpreted as increases in information processing[25,28–30]. Similarly, increases in peak N2 amplitude (or increasingly negative N2 amplitudes) will be interepreted as increases in response inhibition and cognitive control[25].

4.3 Methods

This study is an investigation of prior data[175]. A synopsis of the testing protocol used in the study is described below.

4.3.1 Participants

A total of 24 male participants were recruited and informed assent and consent were obtained. Twelve high school football athletes served as the "contact sport exposed" group. Sampling with replacement was used for one contact athlete who returned for a subsequent year. The "non-contact" group was composed of athletes who participated in non-contact sports which included golf, track and basketball amongst others. This group of athletes had no reported exposure to contact sports throughout the study period. Age in years during preseason measurements was $M = 16.52$, $SD = 0.72$ years for football athletes and $M = 17.01$, $SD = 1.14$ years for non-contact athletes. Height of the football athletes and non-contact athletes was $M = 179.28$, $SD = 6.45$ cm and $M = 176.74$, $SD = 9.27$ cm respectively. Finally, the mean weight of football athletes was $M = 81.25$, $SD = 13.65$ kg and $M = 71.48$, $SD = 10.86$ kg for non-contact athletes.

4.3.2 Testing Protocol

Participants underwent neurophysiological testing at three different time points during the 2013 to 2015 fall (September to November) academic sports season. The first measurement was prior to the start of the season. The second was during the season and the final measurement was completed 23.5±19.8 days from the final session of the season. All athletes completed a detailed questionnaire (Appendix A) at baseline which contained FITBIR TBI Common Data Elements (e.g. age, height, weight) as well as other variables of interest (e.g. medications, caffeine use, sleep, family history of migraines).

Participants were excluded from the study if they had known neurological disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), learning disabilities, concussion or traumatic brain injury (TBI) in the previous 6 months or during the course of the study. Participants were also excluded from this study if they had a history of skull fractures, brain bleeds or any other underlying brain condition.

4.3.3 Instrumentation

4.3.4 Health-Related Quality of Life

The Health Behavior Inventory (HBI), Satisfaction with Life Scale (SWLS) and symptom inventory were utilized as the primary assessments of health-related quality of life at all three time points throughout the course of the season. HBI and SWLS scores were summed into their respective components (Cognitive and Somatic items in the HBI).

4.3.4.1 Satisfaction with Life Scale (SWLS)

The Satisfaction with Life Scale is a 5-item survey utilizing a 7-point Likert scale that ranges from 1 "strongly disagree" to 7 "strongly agree". Values from each item are added to obtain one aggregated score. The SWLS has been shown to represent a subject's satisfaction with life as a whole[176].

4.3.4.2 Health Behavior Inventory (HBI)

The Health Behavior Inventory (HBI) is a 20-item survey utilizing a 9-point Likert scale that ranges from "never" to "often". It has two components: 1) a Cognitive item list and 2) Somatic item list. Higher scores reflect lower participant perceptions of Health Related Quality of Life[177,178].

4.3.5 Demographics Questionnaire

Participants were also questioned on their history of neurological disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), learning disabilities, concussion or traumatic brain injury (TBI).

4.3.6 Event-Related Potentials (ERP)

Electrophysiological measurements were also taken where athletes completed an Auditory Oddball and Go/No-Go task. The subject of this investigation is to analyze Go/No-Go data, Auditory Oddball results will be analyzed elsewhere. During the task subjects were presented tones every 1000-2000 ms. Subjects were instructed to depress a button whenever a target tone (2000 Hz) and inhibit non-target tones (1000 Hz). Non-target tones were presented with a probability of 20% and targets were be

presented with a probability of 80%. All data were collected in accordance to the procedure outlines in the Geodesic Sensor Net Technical Manual[179]. Measures of head circumference were taken and each participant was fitted with an appropriately sized cap. International 10/20 system locations were deduced using Luu and Ferree[179]. Raw data were imported into EEGLab and subsequently filtered with a 1.5 Hz low pass and 40 Hz high pass filter. Bad channels were rejected using built-in tools and later interpolated. Once completed, data were referenced to the average electrode reference.

Event-related potentials, derived from electroencephalography, are phase locked potentials occurring endogenously in the brain[126] related to external events. Components may be phased locked to a stimulus (e.g. N2, P3) or the response (e.g. CRN, ERN, Pe). The Go/No-Go task has been shown to elicit P3 components within both No-Go and Go trials however during No-Go P3 has a larger amplitude and latency[207]. Additionally, the N2 component may only be present in No-Go trials[207]. Epochs were analyzed to confirm the absence of overlap between trial types There was a total of four trial types within the Go/No-Go task (Table 4.1 below).

Table 4.1: ERP Trial Type Abbreviations

Trial Type	Abbreviation
Correct/Go	GoC
Incorrect/Go	GoI
Correct/No-Go	NgC
Incorrect/No-Go	NgI

The term "measurement" will be used to refer to an individual ERP recording. For example, a given participant would have three measurements coded as a within-subjects factor with three levels coded as "time":

1. Pre-season
2. Mid-season and/or
3. End of season

4.3.6.1 Component Definitions

N2 and P3b mean amplitude was calculated by computing the mean in an area of 25ms surrounding the local peak amplitude for each measurement. The following criteria were used for each respective ERP component. P3b utilized electrodes CPz and Pz within 280 to 650ms after stimulus onset. While N2 utilized electrodes FCz and Fz within 150 to 350ms after stimulus onset.

4.3.7 Epoch Extraction

Stimulus-locked epochs were excluded if they overlapped with another event within the range of 100ms before and 1 second after stimulus onset. This resulted in all Go/Incorrect (GoI) trials being removed. Baseline corrections were computed for each epoch type using the 100ms of EEG data prior to stimulus onset. Mean amplitude was defined as the mean of amplitude values within 25ms of the local peak amplitude within each component's time window. Whereas peak local latency was defined as the time where amplitude measures reached its local maxima or minima.

4.3.8 Head Impact Metrics

All football athletes were equipped with a Riddell Revolution Speed helmet in which a Head Impact Telemetry System (HITS, Simbex, Lebanon, NH) encoder was embedded. Each encoder is composed of six single-axis accelerometers measuring at 1 kHz. If data from one accelerometer exceeded 14.4g, data 8 milliseconds before

the 14.4g threshold and 32 milliseconds after, were stored internally. Impacts were recorded during both practice and game sessions throughout the sports season. The system recorded both the location and magnitude of each impact. Aberrant impacts (e.g. athlete throwing his helmet on the ground) were automatically filtered or manually removed prior to subsequent analyses, as were impacts with linear accelerations over 200g. Resultant linear and rotational acceleration for each impact were time stamped and recorded and the following head impact metrics were extracted at both mid-season and end-of-season: maximum linear acceleration, maximum rotational acceleration (largest force of a singular impact). In addition, cumulative values for the Gadd severity index (GSI), head injury criterion (HIC15), Head Impact Technology severity profile (HITsp) as well as cumulative linear and rotational acceleration were computed. Impact density[208] metrics (linear and rotational) were calculated using the baseline ERP test date as the initial time point. Impact density was defined as:

$$\text{Impact Density} = \sum_{\text{i=1}}^{\text{n}} \frac{\text{Acceleration}_{\text{i}}}{\text{Time from ERP Measurement}_{\text{i}}}$$

Note: Acceleration can be linear (Units in g/sec) or rotational (Units in rad/s/s/s).

4.4 Statistical Analyses

Linear mixed methods, an alternative to general linear models, have become increasingly suggested with ERP data[209–213]. Linear mixed effects (LME) model allow investigators to resolve the issue of independence among repeated measures by controlling for individual variation among participants. This is accomplished by adding research participants as a random effect within the model . Essentially, the inclusion of subject as a random effect in the model assumes that each participant has a unique intercept, or "baseline", for each variable[211]. This method also has also been

utilized to address the high level of correlation of electrophysiological components (e.g. ERN[214]) amongst subjects.

R and the lme4[215] package were used to perform linear mixed effects analysis of the relationship between each ERP component and condition. Time, concussion history, HRQOL scores, athlete type and the interaction term between time and athlete type (contact vs non-contact) were entered as fixed-factors. Subject ID and electrode number (when applicable) were entered as random intercepts. Visual inspection of residual plots did not reveal any obvious deviations from homoscedascity or normality. P-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question. An alpha level of .05 was used for all tests.

A second set of analyses were performed uniquely with contact sport athletes using HITS data. Since baseline measures were completed prior to the first game of the season, there were no impact metrics at baseline. The change in ERP compared from baseline was calculated and used as a dependent variable. Within this model, time, number of prior concussions, change in HRQOL scores, impact metrics and the interaction term between time and impact metrics were entered as fixed-factors. Subject ID and electrode number (when applicable) were entered as random intercepts. These models will analyze the presence of changes that occur across the season and how these changes might be predicated on head impact metrics (e.g. maximum linear acceleration, rotational acceleration, number of impacts).

In both models conditional R^2 ($R^2_{LMM(c)}$) and marginal R^2 ($R^2_{LMM(m)}$)[216,217] are provided in summary tables.

4.5 Results

4.5.1 Demographics

Prior to evaluating changes in electrophysiological data, preliminary descriptive analyses were performed to determine differences between groups in height, weight, age and concussion history. Student's t-test revealed no group differences in weight M = 81.25 [74.35, 88.77] vs. M = 71.48 [65.54, 77.30], $t(20.9) = 1.94$, $p = .066$ kg, height M = 179.28 [175.89, 182.88] vs. M = 176.74 [171.66, 182.02], $t(19.6) = 0.78$, $p = .444$ cm or age M = 16.52 [16.09, 16.91] vs. M = 17.01 [16.41, 17.63], $t(18.6) = -1.26$, $p = .222$ years of age. Based on these findings, demographic variables were excluded from our models.

4.5.2 Concussion History

Student's t-test showed that football athletes had significantly more concussions (composed of both diagnosed and undiagnosed) M = 0.75 [0.33, 1.17] vs. M = 0.17 [0.00, 0.42], $t(15.3) = 2.13$, $p = .050$.

4.5.3 Health-Related Quality of Life (HRQOL)

Descriptive statistics (standard deviation (SD), standard error (SE), 95% confidence interval (CI)) were compiled for each athlete type during pre-season, mid-season and end of season measures. A linear mixed effects model was performed. HRQOL scores, time and athlete type were entered as fixed-factors while subject ID was entered as a random factor. Results from these analyses failed to demonstrate any athlete type or time effect over the course of the season in either the Health Behavior Inventory or Satisfaction with Life Scale.

4.5.4 Event-Related Potentials

Grand average waveforms at the three time points during the season for each athlete type are highlighted for each electrode site in Figure 4.1 to 4.4. A summary of the most significant findings can be found in Table 4.3 and 4.4.

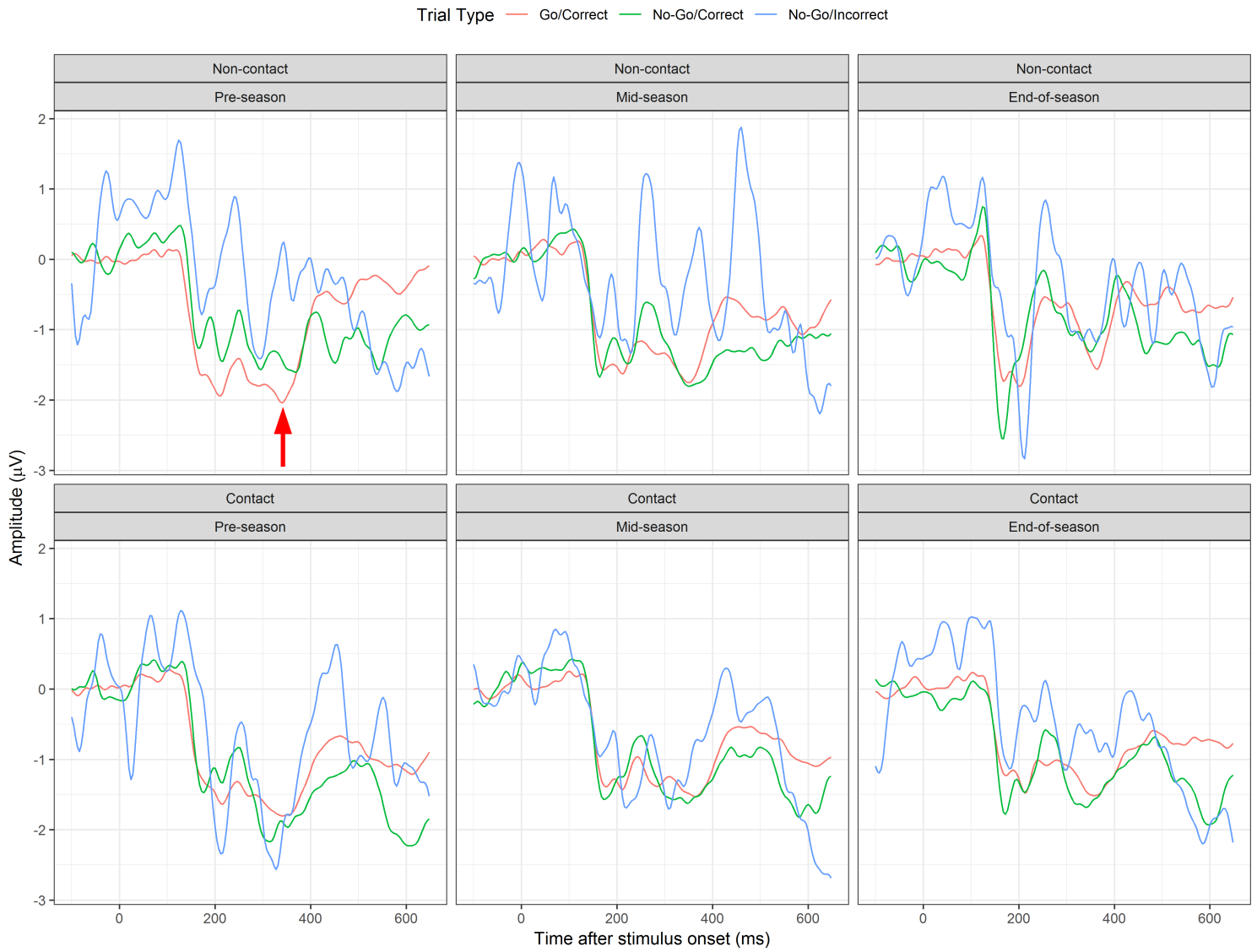

Figure 4.1: Grand Average Waveforms (FCz).

Note: Grand average waveforms are presented for each group and each time point in the season at FCz. Red arrows denote examples of N2. P3b is not noted in this figure since values were extracted from CPz and Pz.

Figure 4.2: Grand Average Waveforms (Fz).

Note: Grand average waveforms are presented for each group and each time point in the season at Fz. Red arrows denote examples of N2. P3b is not noted in this figure since values were extracted from CPz and Pz.

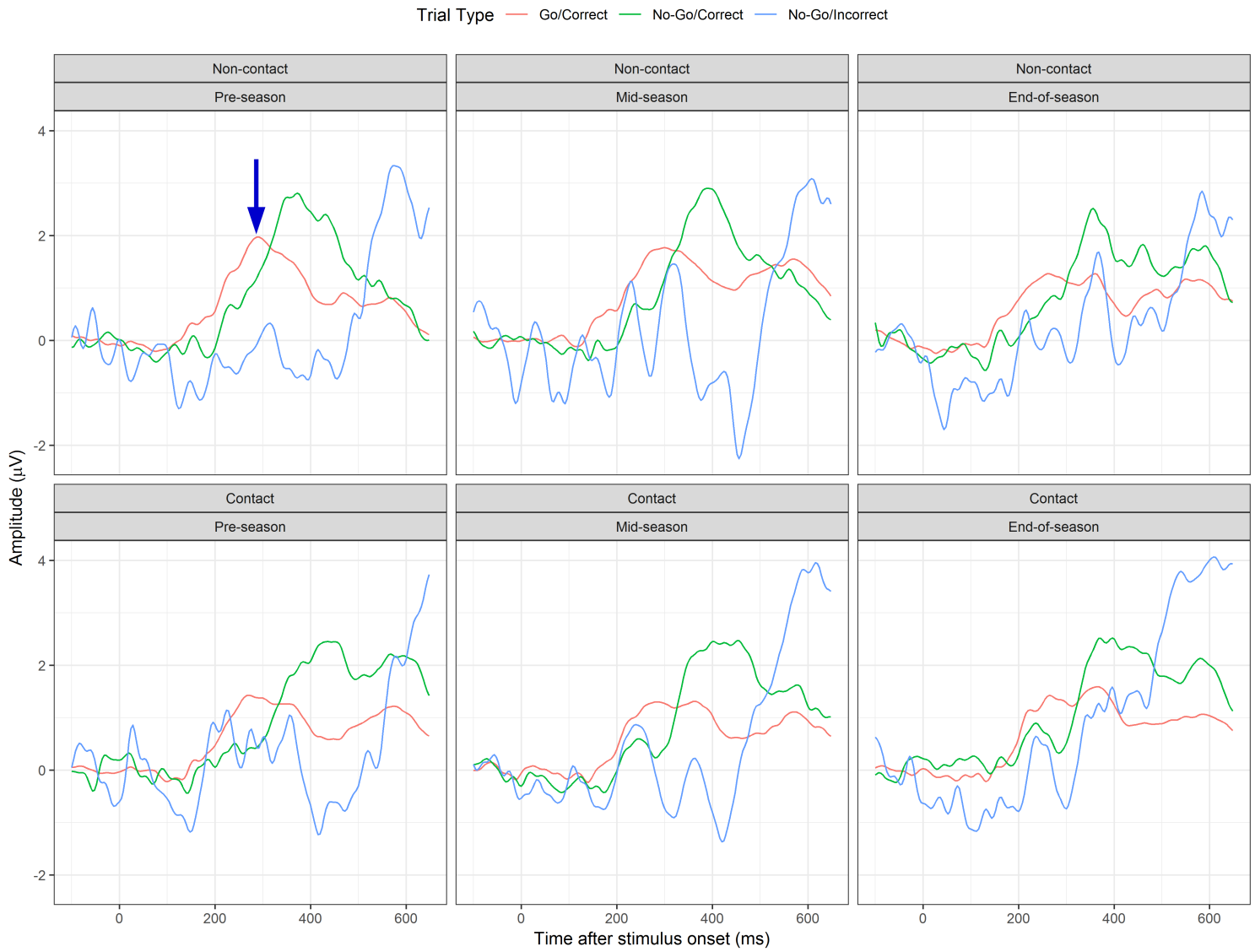

Figure 4.3: Grand Average Waveforms (Cz).

Note: Grand average waveforms are presented for each group and each time point in the season at Cz. Blue arrows denote examples of P3b. N2 components are not noted in this figure since values were extracted from FPz and Fz.

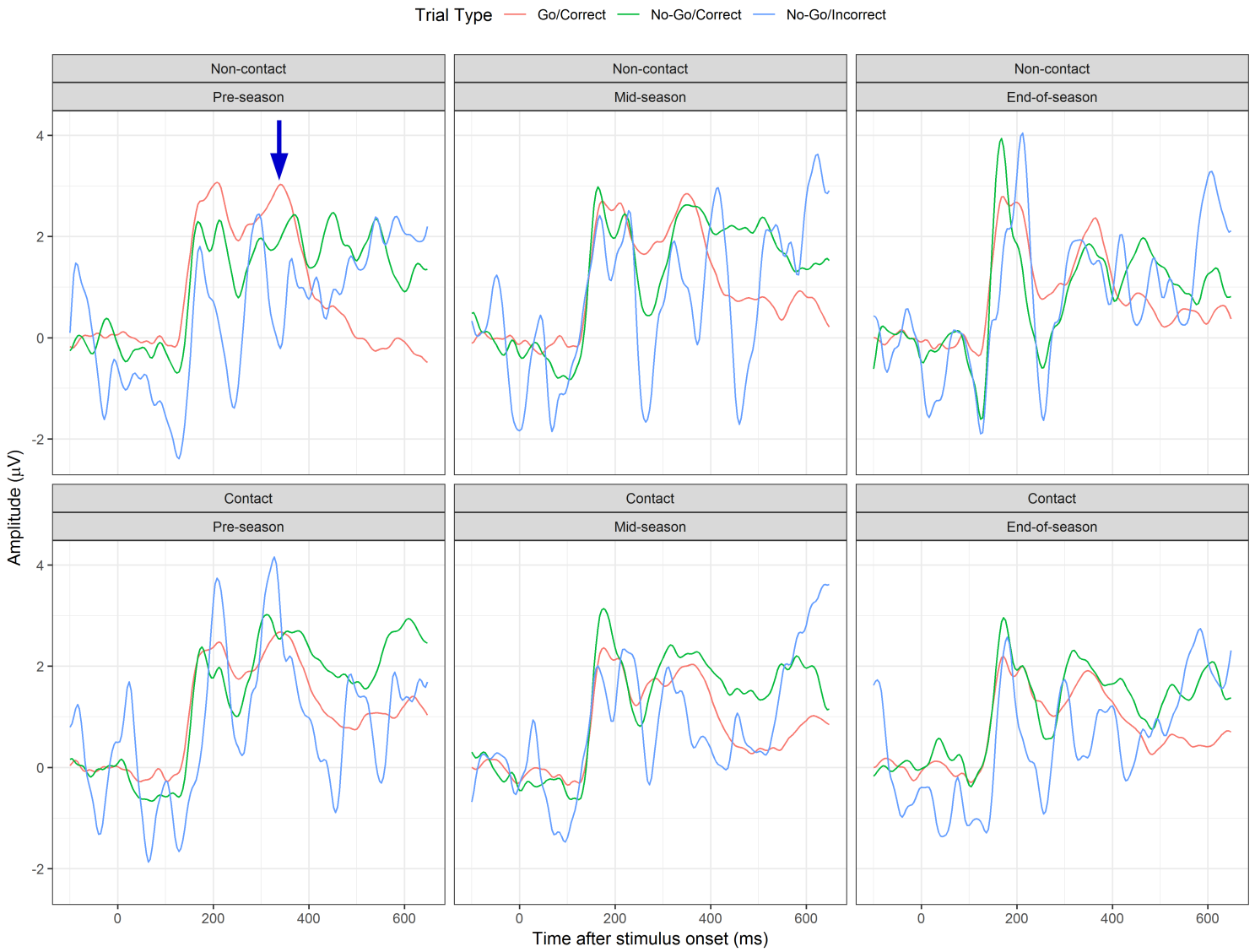

Figure 4.4: Grand Average Waveforms (Pz).

Note: Grand average waveforms are presented for each group and each time point in the season at Pz. Blue arrows denote examples of P3b. N2 components are not noted in this figure since values were extracted from FPz and Fz.

4.5.5 P3b

A three-way interaction (Athlete type×Number of undiagnosed concussions×Trial Type) was observed in P3b amplitude during No-Go incorrect trials between number of undiagnosed concussions and athlete type at end-of-season, $t(310) = 3.08$, $p = .002$. Follow up analyses demonstrated that during these trials the non-contact athletes without a history of undiagnosed concussions were the only group to show increases in P3b amplitude over the course of the season, $t(313) = -2.25$, $p = .025$. Finally, P3b latency was significantly longer in No-Go trials compared to Go trials, $t(309) = 3.47$, $p < .001$.

4.5.5.1 Changes in P3b from baseline in Contact athletes

As previously mentioned, the change in ERP components from baseline was calculated at both mid-season and end-of-season. A significant interaction between differences in P3b amplitude from baseline measures, linear impact density and the number of concussion was observed, $t(46) = -2.02$, $p = .050$. An evaluation of the interaction revealed that contact athletes without a concussion history showed increases in peak P3b amplitude over the season. Yet, individuals with a concussion history showed smaller increases in P3b amplitude as function of increasing linear impact density, $t(46) = -2.90$, $p = .006$. This effect was only present once the threshold of 0.0167 g/s in linear impact density was exceeded.

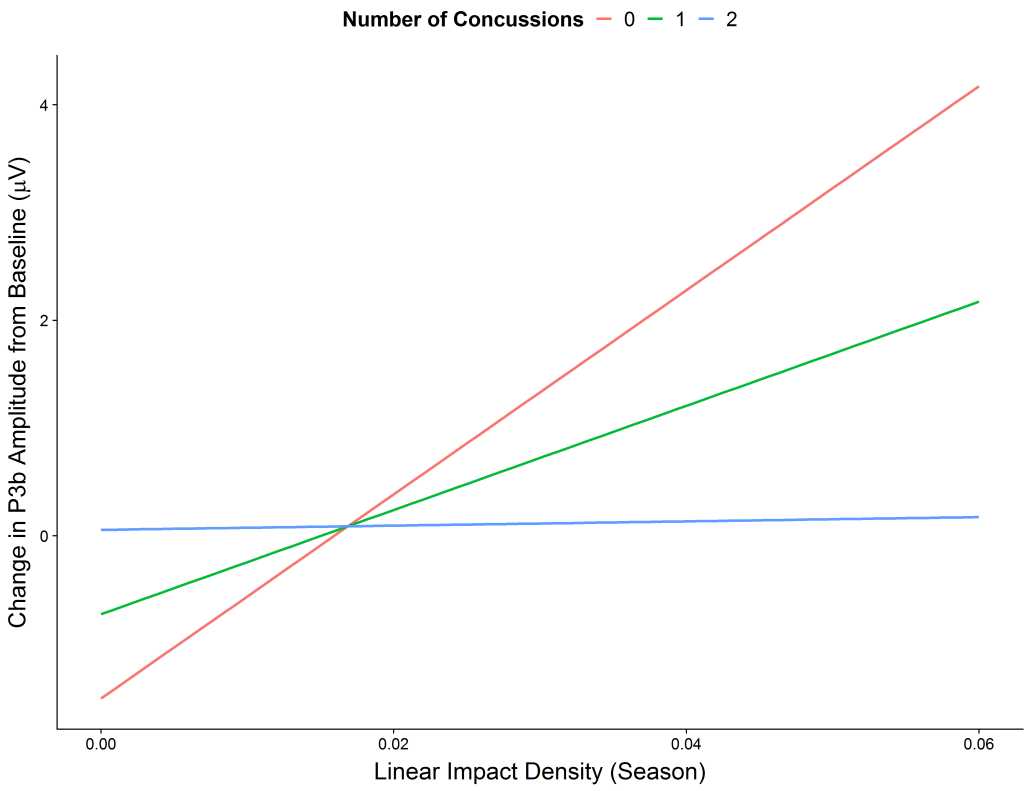

Figure 4.5: Changes in P3b Amplitude from Baseline as a Function of Linear Impact Density

4.5.6 N2

A three-way interaction was observed in N2 amplitude between trial type, number of undiagnosed concussions and athlete type, $t(309)$ = -3.03, p = .003. Post-hoc comparisons demonstrated that non-contact athletes with 0 or 1 undiagnosed concussion showed stable measures of N2 amplitude over the course of the season during No-Go/Correct trials. However, contact athletes with one undiagnosed concussion showed increases in N2 amplitude compared to contact-sport athletes without a history of undiagnosed concussions within the same condition.

The same three-way interaction between undiagnosed concussion history and athlete type and N2 amplitude was observed during the No-Go/Incorrect trials, $t(310)$ =

-2.56, $p = .011$. During incorrect responses in No-Go trials, an interaction between athlete type and time was also observed in measures of N2 amplitude at mid-season, $t(59) = 3.79$, $p < .001$, and end of season, $t(57) = 3.75$, $p < .001$ was noted. In both cases, N2 amplitude measures decreased (became increasingly positive) in contact athletes. These are demonstrated as bar graphs in Figure 4.6

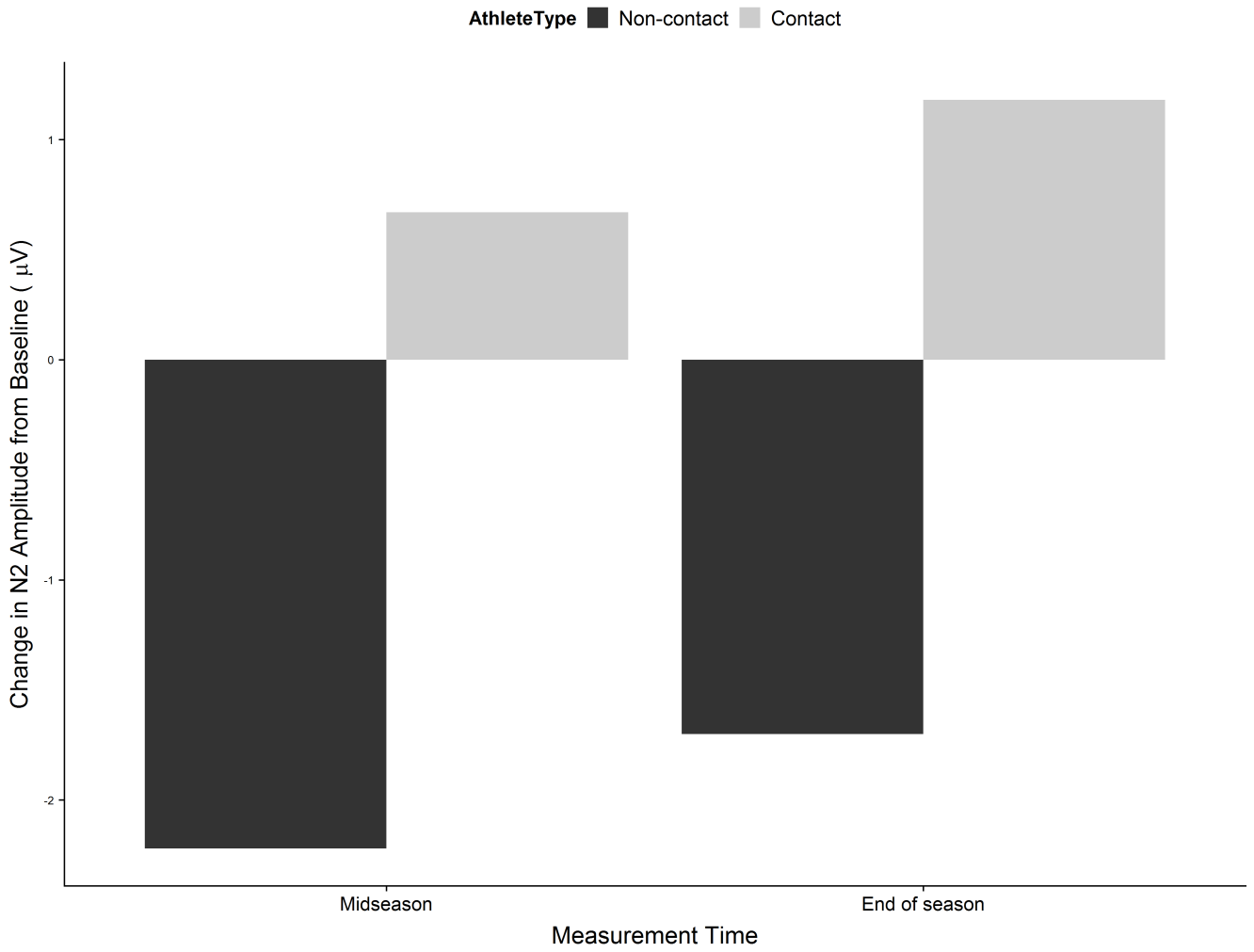

Figure 4.6: Changes in N2 Amplitude from Baseline during No-Go Incorrect Trials

4.5.6.1 Changes in N2 from baseline in Contact athletes

In a manner similar to the findings noted in P3b, a three-way interaction between concussion history (diagnosed and undiagnosed) and impact density was observed for changes in N2 amplitude from baseline. Once again, a threshold needed to be exceeded in impact density for this change to occur which was evident based on the interaction between both linear, $t(14) = 2.30$, $p = .037$, and rotational, $t(14) = 2.25$, $p = .042$, impact density with the number of prior concussions. For rotational impact density this threshold was approximately 0.79 rad/s/s/s (Figure 4.8) and for linear impact density the threshold was 0.0187 g/s (Figure 4.7).

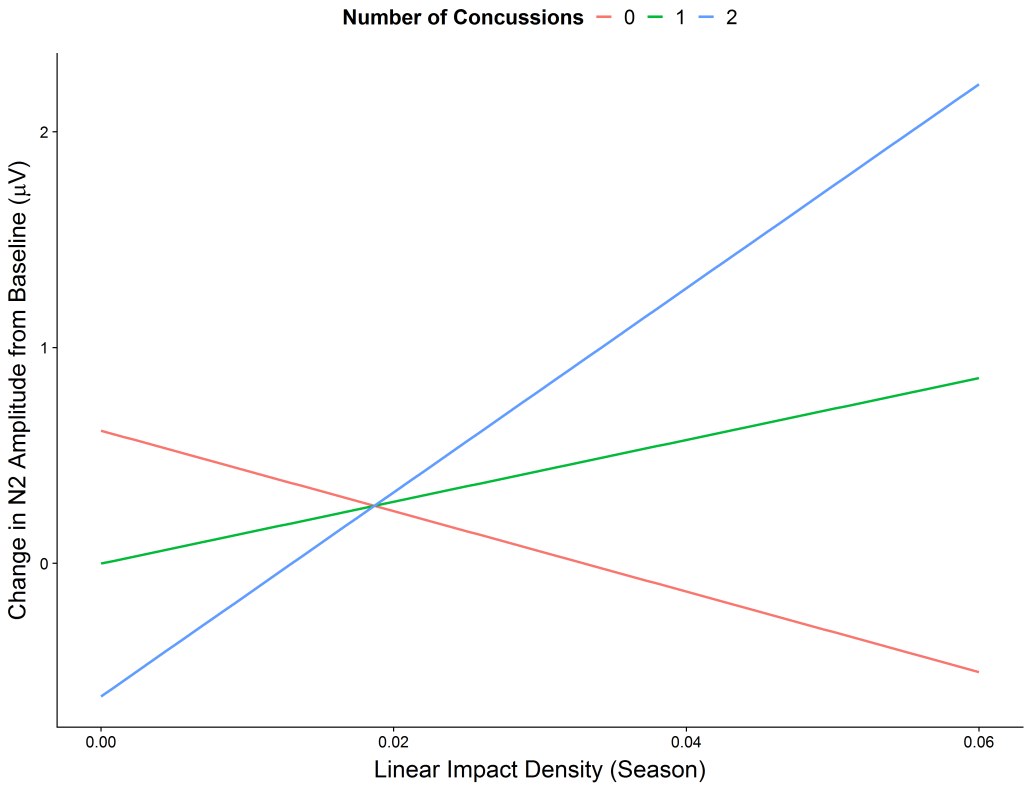

Figure 4.7: Changes in N2 Amplitude from Baseline as a Function of Linear Impact Density

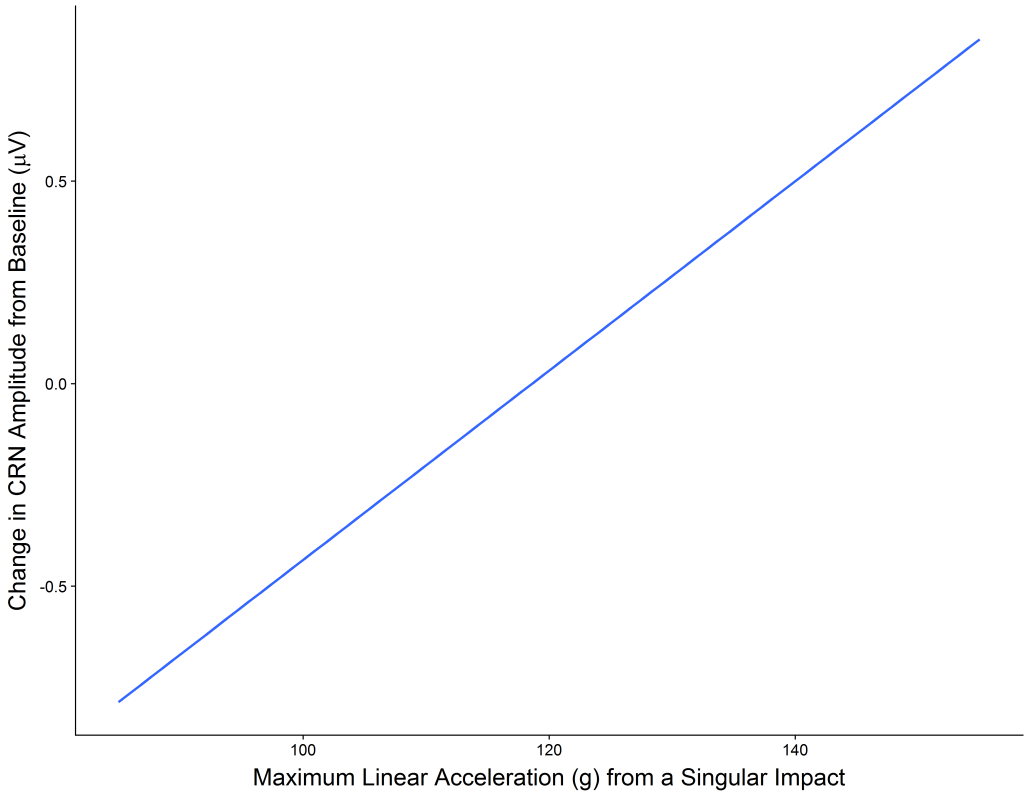

Figure 4.8: Changes in N2 Amplitude from Baseline as a Function of Rotational Impact Density

4.5.7 Percentage of Errors by Trial Type

A summary of the mean and standard deviations for the percentage of errors during Go and No-Go trials is provided in Table 4.2.

Table 4.2: Percentage of Errors by Condition

AthleteType	Percentage of Errors (Go Trials)	Percentage of Errors (No-Go Trials)
Contact	2.71±2.68	15.71±11.78
Non-contact	3.81±5.71	12.2±9.22

There was a significant effect of the number of prior concussions on the percentage

of errors but only within the Go trials, $F(1, 63) = 7.93$, $p = .006$. The percentage of errors during Go trials showed no associations with athlete type. There was a 5% increase in the number of errors within this condition for athletes with two previous concussions vs athletes who had no concussion history.

4.5.8 Results Summary

Table 4.3: Results Summary: Contact vs Non-Contact Athletes

Component	Test	Result	$R^2_{LMM(c)}$	$R^2_{LMM(m)}$
P3b amplitude	Athlete type×Undiagnosed Concussions×Trial Type	t(310)=3.08, p=.002	0.34	0.66
P3b latency	Trial Type	t(309)=3.47, p<.001	0.29	0.47
N2 amplitude	Athlete type×Undiagnosed Concussions×Trial Type	t(309)=-3.03, p=.003	0.26	0.58

Note: $R^2_{LMM(c)}$: Conditional R^2; $R^2_{LMM(m)}$: Marginal R^2

Table 4.4: Results Summary: Head Impact Metrics in Contact Athletes

Component	Test	Result	$R^2_{LMM(c)}$	$R^2_{LMM(m)}$
P3b amplitude	Linear Impact Density×Concussion History	t(46)=-2.02, p=.050	0.19	0.29
N2 amplitude	Linear Impact Density×Concussion History	t(14)=2.30, p=.037	0.43	0.62
N2 amplitude	Rotational Impact Density×Concussion History	t(14)=2.25, p=.042	0.44	0.65

Note: $R^2_{LMM(c)}$: Conditional R^2; $R^2_{LMM(m)}$: Marginal R^2

4.6 Discussion

The objective of the current study was to determine if changes in electrophysiological components existed after a season of contact-sport exposure within two groups of high school athletes. Surprisingly, neither of the HRQOL measures (e.g. SWLS, HBI) showed any association with changes in ERP components that occurred over the course of the season or between athlete groups even when concussion history was taken into consideration. Although outside of the scope of the original purpose of our study we found several interactions between athlete type, concussion history and head impact metrics across ERP components.

P3b amplitude has been previously linked to working memory[218,219]. A recent report indicated[12] that changes in working memory were correlated with the number of head impacts and peak rotational acceleration in football players. Within our study these impact metrics failed to demonstrate associations with P3b amplitude.

P3b amplitude showed no significant differences during correct responses between contact and non-contact athletes in Correct/Go trials over the course of the season. Similar results were observed in P3b amplitude during No-Go trials. These results were inconsistent with prior work by Moore et al.[220], who observed greater decreases in P3b amplitude in contact sport athletes in comparison to non-contact sport athletes yet to a lesser degree than contact athletes without a concussion history. Non-contact athletes with a concussion history were not included in the study.

We did however, observe decreases in P3b amplitude as a function of concussion history and linear impact density threshold in our contact athletes. These results were consistent with prior work in concussed athletes[27,221–225] which have also reported significant decreases in P3b amplitude as a function of concussion history. Collectively our P3b amplitude findings indicate that concussion history in conjunction with linear

impact density hamper information processing within contact athletes.

Changes in P3 latency have been noted in prior work with concussed athletes[134–137]. In one particular study, athletes' with three or more concussions showed latency increases of approximately 45ms[135]. In this study, P3 latency did not increase as a function of an athlete's number of diagnosed concussions. Rather, this association was observed as a function of N2 amplitude. Our ability to observe these changes may be due in part to the homogeneity within our sample which was composed uniquely of males within a specific age-range. The difference between concussed athletes sampled in prior work and non-concussed football athletes used in this investigation may also be responsible for the lack of findings in P3b latency.

Changes in N2, a measure of executive function[226] and response inhibition[26,227], due to concussion history have been mixed. Ledwidge and Molfese[228] reported larger N2 amplitudes in athletes with a concussion history using a two-tone auditory oddball task. In contrast, Broglio et al.[27] reported smaller N2 amplitudes using the three stimulus oddball task. Additional research by Gosselin et al.[229], Gaetz et al.[230] and Moore[231] found no differences based on concussion history. Discrepancies between these studies may be attributed to differences between task and exclusion criteria. This was highlighted in work by Moore et al.[232] who investigated changes in electrophysiological measures using three separate tasks: the visual oddball task, switch task and flanker task. They found greater N2 amplitudes and latency in participants with a concussion history but only while using the switch task. The visual oddball and flanker task both failed to demonstrate these differences in N2 amplitude and latency.

The alterations reported in this study are consistent with reports by Moore et al.[220] who reported that contact sport athletes were shown to have alterations in event-related potential components greater than non-contact sport athletes yet to a lesser

degree than contact athletes without a concussion history. Specifically, N2 amplitude decreased over the course of the season in contact athletes with a history of undiagnosed concussions. This decrease in N2 amplitude was not observed in athletes without a reported undiagnosed injury or non-contact athletes with an undiagnosed concussion. In our subsequent analyses in football athletes we showed that decreases in N2 amplitude could be predicted by selected impact metrics (linear and rotational impact density). Detriments within this index of executive function were only present once a threshold in impact metrics had been eclipsed (linear impact density>0.0167 g/s). These findings indicate that contact athletes show decreasing cognitive control and response inhibition in comparison to non-contact athletes. These differences are enlarged once a contact athlete surpasses a threshold in linear impact density.

The relationship between diagnosed and undiagnosed concussive injuries remains unclear in the context of ERP indices despite other forms of neuroimaging have shown differences between diagnosed and undiagnosed concussive injuries. Although previous investigations using transcranial magnetic stimulation (TMS)[233] have shown that unreported/undiagnosed concussive injuries during adolescence could inhibitory networks. These networks should be highlighted in a task such as the Go/No-Go yet we failed to demonstrate an association between the number of errors and undiagnosed concussion history.

Our results showing a clear association between ERP indices with head impacts over a period of time align with animal models. Wherein football athletes in our study, much like the rats in prior works[191–193], given longer recovery times failed to demonstrate detrimental effects from repeated subclinical head impacts. This narrative is in contrast to some reports claiming that RHSI are detrimental under all circumstances[234–236]. Our results seem introduce a caveat to these reports, a threshold in impacts over time must be exceeded.

Since the neuroimaging methods used in the animal models presented have yet to be developed for use in humans, a multidisciplinary approach utilizing head impact telemetry, functional magnetic resonance and event-related potentials shows the most promise to distinguish the precise thresholds associated with declines in brain function due to repeated subclinical head impacts.

4.6.1 Limitations

The homogeneity between our two groups (e.g. similar age, same school and gender) may have increased our ability to observe changes. Additionally, the link between ERP indices and head impacts reported here may differ if exposure times greater than one season were investigated.

4.7 Conclusion

These data demonstrate differential changes over the course of the season between football and non-contact athletes as well as concussion history which may present clinically as decreases in cognitive control, response inhibition, information processing and working memory. They also suggest that specific ERP components (e.g. N2, P3b) may be associated with both contact-sport participation and concussion history. Measures of executive function (N2) showed a greater association with undiagnosed concussions. A better understanding of these relationships could elucidate specific differences, between time course and cognitive alterations that occur during concussion recovery and repeated subclinical head impacts.

Our subgroup analysis of HITS data in our contact athletes demonstrated that decreases in electrophysiological indices of attention resource allocation, executive function and response inhibition was compounded with increasing levels of concussion

history. These deteriorations were only present once a threshold in head impact metrics was exceeded. No changes, as a function of concussion history, was found in contact athletes who failed to reach this critical threshold in impact metrics. Based on these results, future work in this area may wish to avoid using contact sport participation without direct measure of head impact exposure as a proxy for subclinical head impacts.

Finally, the association between undiagnosed and diagnosed concussions remains poorly understood. Yet, based on our findings individual components may show altering levels of sensitivity to each of these factors. A follow-up investigation of these data will attempt to use response-locked electrophysiological indices to further explain this relationship in greater detail.

CHAPTER 5

Project 2: The Association Between Head Impact Metrics, Contact Sports and Response-locked Electrophysiological Indices of Brain Function

5.1 Abstract

Event-related potentials have emerged as a powerful tool in evaluating electrophysiological changes associated with sports-related concussion. The contribution of response-locked components has received little attention as majority of electrophysiological investigations on concussion and repeated subclinical head impacts have focused on stimulus-locked components (e.g. N2, P3). The goal of this study is to examine whether changes in neural function, as measured via response-locked event-related potentials, vary as a function of advanced head impact metrics, contact-sport exposure and concussion history over the course of one season of exposure. **Methods:** Over a three-year period, high school football athletes were recruited to take part in the study and equipped with the head impact telemetry system (HITS) which continuously monitored head impact counts, magnitude and location throughout the fall football season. These data were used to calculate a variety of head impact metrics.

Comparisons were made to age-matched non-contact athletes (n=12). Electrophysiological measures were also recorded using a 256 dense array electroencephalogram during a Go/No-Go task. These measures were taken before the start of the season, at mid-season and at the end of the season. **Results:** Attenuated levels in error monitoring indices (ERN) were seen as a function of undiagnosed concussions in both contact and non-contact athletes. Decreases in Pe amplitude, a measure of cognitive control, were observed as a function of increasing number of undiagnosed concussions but only in contact athletes. In a secondary analysis, containing only contact athletes, changes in ERN and Pe amplitude from baseline were significantly predicted by measures of linear and rotational impact density over the season. Other cumulative impact metrics (e.g. GSI, HIC15, HITsp) showed no association. **Conclusion:** Overall the results from this investigation demonstrate a significant association between varying levels of error monitoring and cognitive control indices with undiagnosed concussion history in both contact and non-contact athletes. The results are frame worked in the context of emerging neuroimaging literature and parallels to current magnetic resonance imaging studies are discussed.

5.2 Introduction

In the United States approximately 8 million athletes play in organized sports. Football is the most popular program with nearly 25% of high school boys participating (over 1 million participants) according to the National Federation of State High School Associations data from 2014-15. Not surprisingly, American football is responsible for over a third of sports-related concussions in team sports[237]. In high school football, athletes sustain an average 652 impacts over the course of a season[238] and research has demonstrated detrimental effects resulting from impacts below the threshold of concussion[239–242]. These impacts termed “repeated subclinical head

impacts" (RHSI), have been linked to long-term health detriments such as chronic traumatic encephalopathy (CTE)[8,189,243,244].

Associations between neuroimaging data and RSHI have largely relied on self-reported exposure of head impacts, such as "years playing contact sports", to infer the deleterious effect of head impacts on the brain. These studies have provided some insight, yet a more direct and objective measure of head impacts is required in order to properly assess the relationship between brain alterations and biomechanical insults.

In recent years, investigators have used telemetry systems in order to obtain a measure of head impact frequency and magnitude to corroborate neuroimaging data following exposure to subclinical head impacts and concussion. Diffusion tensor imaging (DTI), an MRI-based technique based on water's diffusion rate within tissues, has been applied to the study of repeated subclinical head impacts. Bazarian et al.[12] found significant decreases in fractional anisotropy (FA), which is believed to reflect myelination in white matter[245], in non-concussed football athletes which persisted after 6 months of non-contact rest. This same sample demonstrated alterations in working memory that were correlated with multiple head impacts as measured using telemetry systems. The changes from pre-season to end of season represented approximately a 1% change.

Subsequent studies by Chun et al.[246] and Breedlove et al.[13], similarly noted a significant relationship between the number of impacts and changes in fractional anisotropy. In another fMRI study using head impact telemetry, McAllister et al.[247] reported that number of impacts, HITsp and peak linear acceleration two weeks prior to neuroimaging measurement were correlated with white matter changes in the amygdala over the season. Hippocampal changes were associated with number of hits, linear and rotational accelerations but only when these impact metrics were calculating within the 14 days prior. The association was not present if measures throughout the

entire season were used. The importance of these findings is unquestionable yet in comparison to other forms of neuroimaging, such as electroencephalography (EEG), fMRI has a higher cost, less temporal resolution and is impossible to administer on the field.

Event-related potentials (ERP) are phase locked potentials derived from EEG signals occurring endogenously in the brain[126]. By evaluating minute fluctuations in voltage, stemming from postsynaptic potentials within the brain during internal or external events, researchers are able to investigate specific electrophysiological responses related to cognitive processes ranging from vision, motor control and executive function amongst others. ERP components can be divided into two specific classes of components based on whether they are time-locked to the presentation of stimuli (i.e. stimulus-locked components) or a participant's response (i.e. cue-locked, response-locked or target-locked).

Event-related potentials offer unique advantages over other neuroimaging modalities as they can be used in parallel with clinical exams, the current gold standard for concussion assessment, to evaluate cognitive changes. Despite little research on RHSI with ERP, we can infer from work in sports-related concussion where several review papers[15,248,249] have outlined the promise of electrophysiological measures to elucidate changes in neural functioning post-injury.

Brush et al.[248] conducted the most recent review on the effects of sports-related concussion from the perspective of event-related potentials. Of the twenty papers, published through January 2017, which met inclusion criteria, only four reported response-locked ERP components[250–253]. Despite its sparse use in the evaluation of sports-related concussion, response-locked components have been successfully applied to the study of several clinical populations[254–258]. The authors[248] also emphasize that none of the ERP studies to date on sports-related concussion have been

prospective in nature and recommend a pre-post design to control for confounding risk factors.

Two response-locked components, error-related negativity (ERN) and error positivity (Pe), have been discussed in the context of sports-related concussion. The ERN can be seen in error trials where a distinct negative onset in the ERP activity which peaks at approximately 50ms. The amplitude of the ERN is greatest along the midline frontal and central electrodes[138,139]. Pe is defined by a positive deflection which peaks approximately 200-400ms post-response[259,260]. Although there remains a debate as to the precise underlying mechanisms for each of these components there is a general consensus that the ERN and Pe represent unique error-related functions. It has been suggested that the ERN involves the processing of an error while elevated Pe amplitudes are associated with the awareness of error[18,260,261]. Despite the potential of event-related potentials outlined above, they have yet to be evaluated alongside head impact telemetry systems. The present study fills a gap in the literature by evaluating changes in brain function, normally evaluated in fMRI, using event-related potentials and its relationship with head impact metrics as measured by telemetry systems (HITS). In accordance with the aforementioned works, increasingly negative peak CRN/ERN amplitude will be interpreted as increases in error monitoring processes. Increasingly negative error positivity (Pe) will be interpreted as deficits in error awareness.

5.3 Methods

This study is a retrospective investigation of data[175].

5.3.1 Participants

A total of 24 participants (n=12 contact athletes, n=12 non-contact) were recruited and informed assent and consent were obtained. The "non-contact" group was composed of athletes who participated in noncontact sports which included golf, track and basketball amongst other. This group of athletes had no reported exposure to contact sports throughout the study period. Sampling with replacement was used for one contact athlete who returned for a subsequent year.

Pre-season testing included a demographics questionnaire which contained Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR) TBI Common Data Elements[262] (e.g. age, height, weight) as well as other variables of interest (e.g. medications, caffeine use, sleep, family history of migraines). Demographic information is summarized in Table 5.1.

Table 5.1: Descriptives per Group

	Football	Non-Contact	t	p
n	12	12	-	-
Mean Height (cm)	179.28	176.74	0.78	0.4441
Mean Weight (kg)	81.25	71.48	1.94	0.0662
Mean Age (Years)	16.52	17.01	-1.26	0.2225
Number of Concussions	0.75	0.17	2.13	0.05
Number of Diagnosed Concussions	0.67	0	2.6	0.0246
Number of Undiagnosed Concussions	0.25	0.42	-0.84	0.4088

5.3.2 Event-Related Potentials

Researchers have observed ERN-shaped waveforms during correct response trials[17,263]. Vidal et al.[263] suggested that the presence of the ERN on correct trials may reflect a comparative process which occurs prior to error detection. To alleviate confusion, researchers have termed this CRN, correct-response negativity. Less is known of this negative component following correct responses. Vidal et al.[263] reported that the topographies in the negative deflection following correct and incorrect responses represent the same process. They argue argued that, contrary to Pe, the ERN was not specific to erroneous responses. Noting that during correct trials the (correct) ERN was smaller than during error trials[253]. Although we acknowledge prior works[253,264,265] who have utilized the term "ERN during correct trials", for the purposes of this document we will refer to this as the CRN while the acronym "ERN" will be used exclusively to denote changes that occur during erroneous responses.

High-density event-related potentials were measured while participants (n=24) performed an auditory Go/No-Go task. Stimuli were presented with E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA). The first ERP measurement was prior to the start of the season. The second was during the season and the final measurement was completed 23.5Â±19.8 days from the final session of the season.

The following criteria were used to compute ERN and Pe mean amplitude and latency. ERN amplitude was evaluated by calculating the mean amplitude within a 25ms interval surrounding the most negative going peak at FCz and Fz within 0 to 100 ms[16] post-response onset. Pe was calculated similarly by evaluating a positive going peak at CPz and Pz electrodes within 200 to 500 ms[266,267] post-response.

Response-locked epochs were excluded if they overlapped with another event within the range of 600ms before and 1 second after the onset of a response. Once completed,

the number of epochs for each event type was computed to confirm the presence of a minimum of 8 trials. If a minimum of 8 trials were not present, they were removed from subsequent analysis given results from prior works[268–272]. Based on recent work by Overbeak et al.[260] demonstrating inconsistencies in Pe latency, this metric was omitted from our analyses.

5.3.3 Head Impact Telemetry

Head impact metrics were collected over the course of the season in contact athletes using the Head Impact Telemetry System (HITS; Simbex, Lebanon, NH). Each encoder is composed of six single-axis accelerometers measuring at 1 kHz. If data from one accelerometer exceeds 14.4g, data 8 milliseconds before the 14.4g threshold and 32 milliseconds after, are stored internally. Data were exported from the system and additional head impact metrics were calculated at mid-season and end-of-season. Measures included the Gadd severity index (GSI), head injury criterion (HIC15), Head Impact Technology severity profile (HITsp) as well as cumulative linear and rotational acceleration. Impact density[208] metrics (linear and rotational) were calculated using the baseline ERP test date as the initial time point. Impact density was defined as:

$$\text{Impact Density} = \sum_{\text{i}=1}^{\text{n}} \frac{\text{Acceleration}_{\text{i}}}{\text{Time from ERP Measurement}_{\text{i}}}$$

Note: Acceleration can be linear (Units in g/sec) or rotational (Units in rad/s/s/s).

5.3.4 Statistical Analyses

Our primary analyses used a linear mixed model for repeated measures over the course of the season by athlete type (contact versus non-contact) to evaluate changes

in ERP components. Follow-up analyses for the fixed effects of concussion history (total number of concussions and undiagnosed concussions) where each participant was entered as a random factor were also conducted.

Secondary analyses determined how head impact metrics affected changes from baseline in electrophysiological measures in our sample of football athletes. A linear mixed model was also used with head impact metrics, concussion history and health-related quality of life measures as fixed factors and participant as a random factor. All statistical significance tests were two-tailed with $\alpha = 0.05$. In both models conditional R^2 ($R^2_{LMM(c)}$) and marginal R^2 ($R^2_{LMM(m)}$)[216,217] are provided in summary tables.

5.4 Results

5.4.1 Event-Related Potentials

Grand average waveforms during the three measurements within the season for each athlete type are highlighted for each electrode site in Figure 5.1 to 5.4. A summary of the most significant findings can be found in Table 5.2 and 5.3.

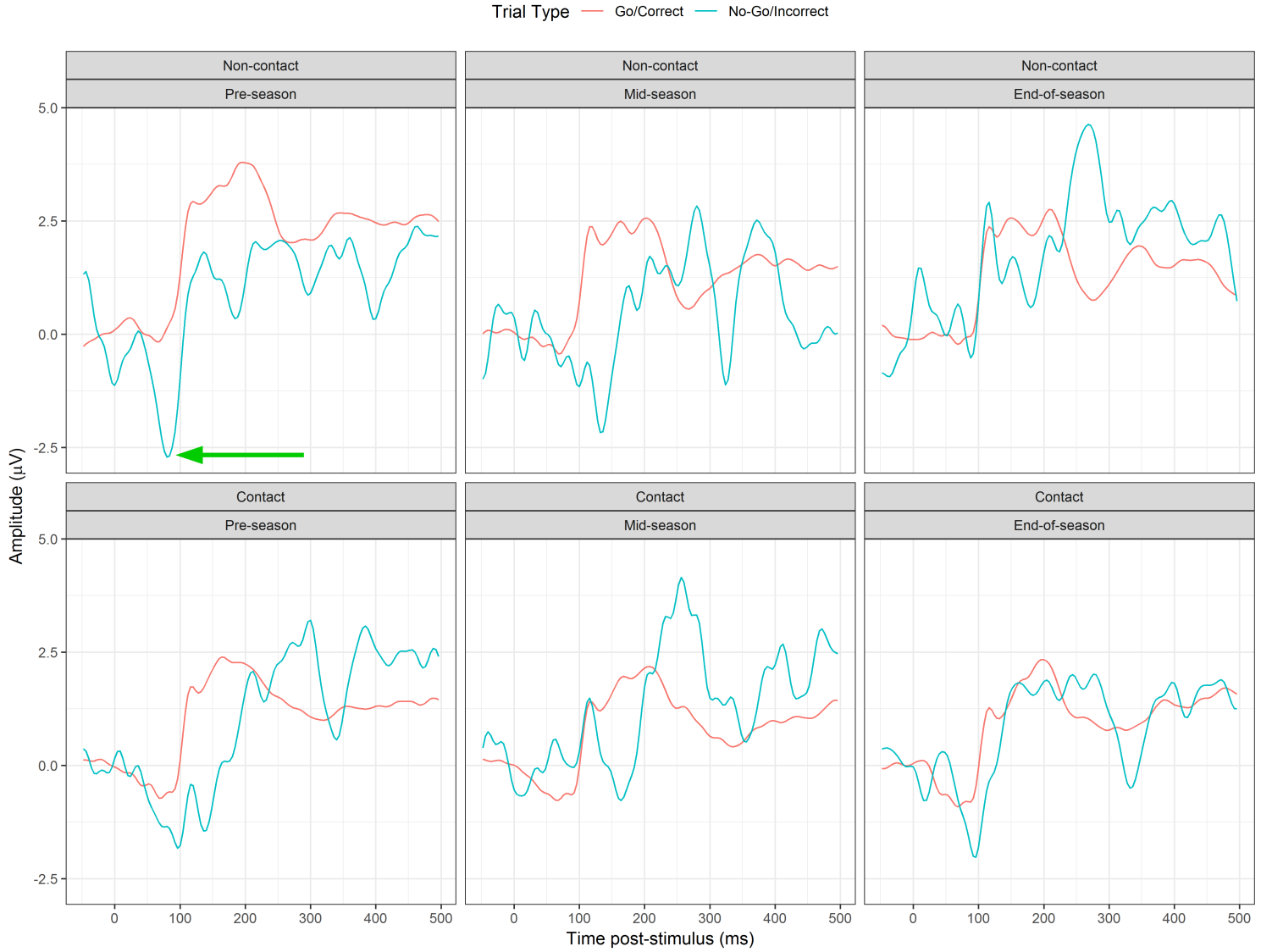

Figure 5.1: Post-Response Grand Average Waveforms (FCz).

Note: Grand average waveforms are presented for each group and each time point in the season at FCz. Green arrows denote an example of the ERN component. Pe is not noted in this figure since values were extracted from CPz and Pz.

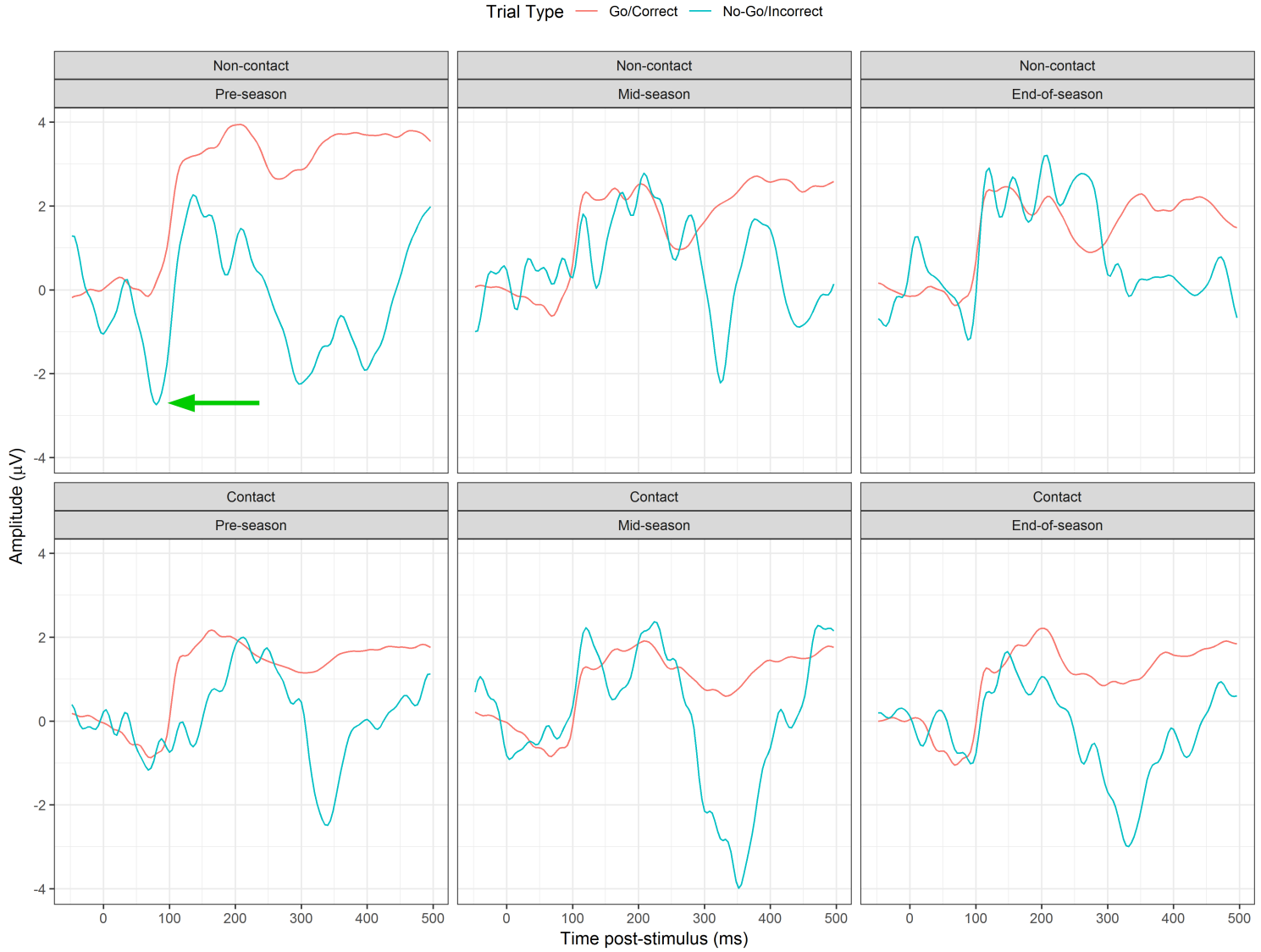

Figure 5.2: Post-Response Grand Average Waveforms (Fz).

Note: Grand average waveforms are presented for each group and each time point in the season at Fz. Green arrows denote an example of the ERN component. Pe is not noted in this figure since values were extracted from CPz and Pz.

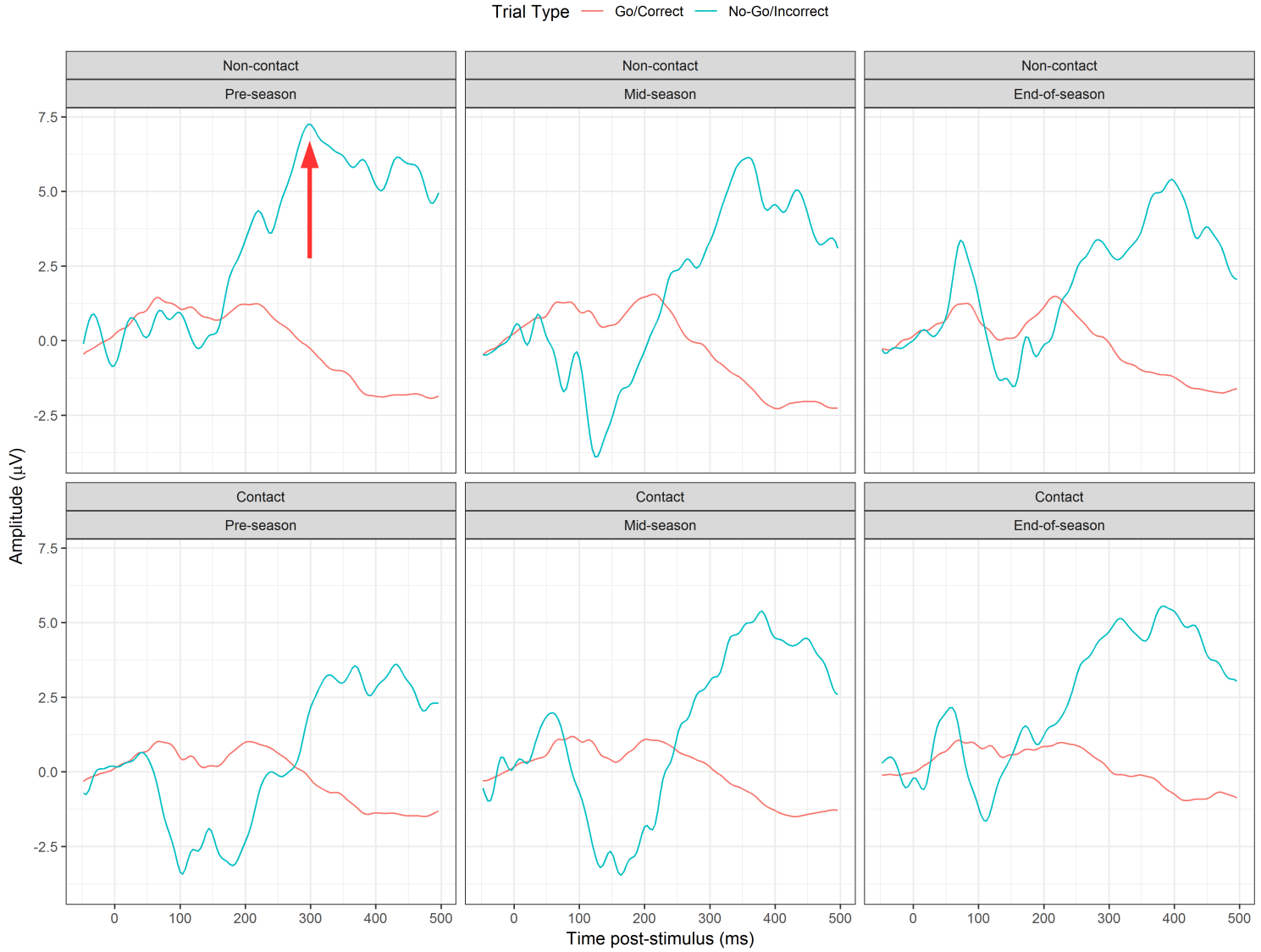

Figure 5.3: Post-Response Grand Average Waveforms (Cz).

Note: Grand average waveforms are presented for each group and each time point in the season at Cz. Red arrows denote an example of the Pe component. ERN is not noted in this figure since values were extracted from FPz and Fz.

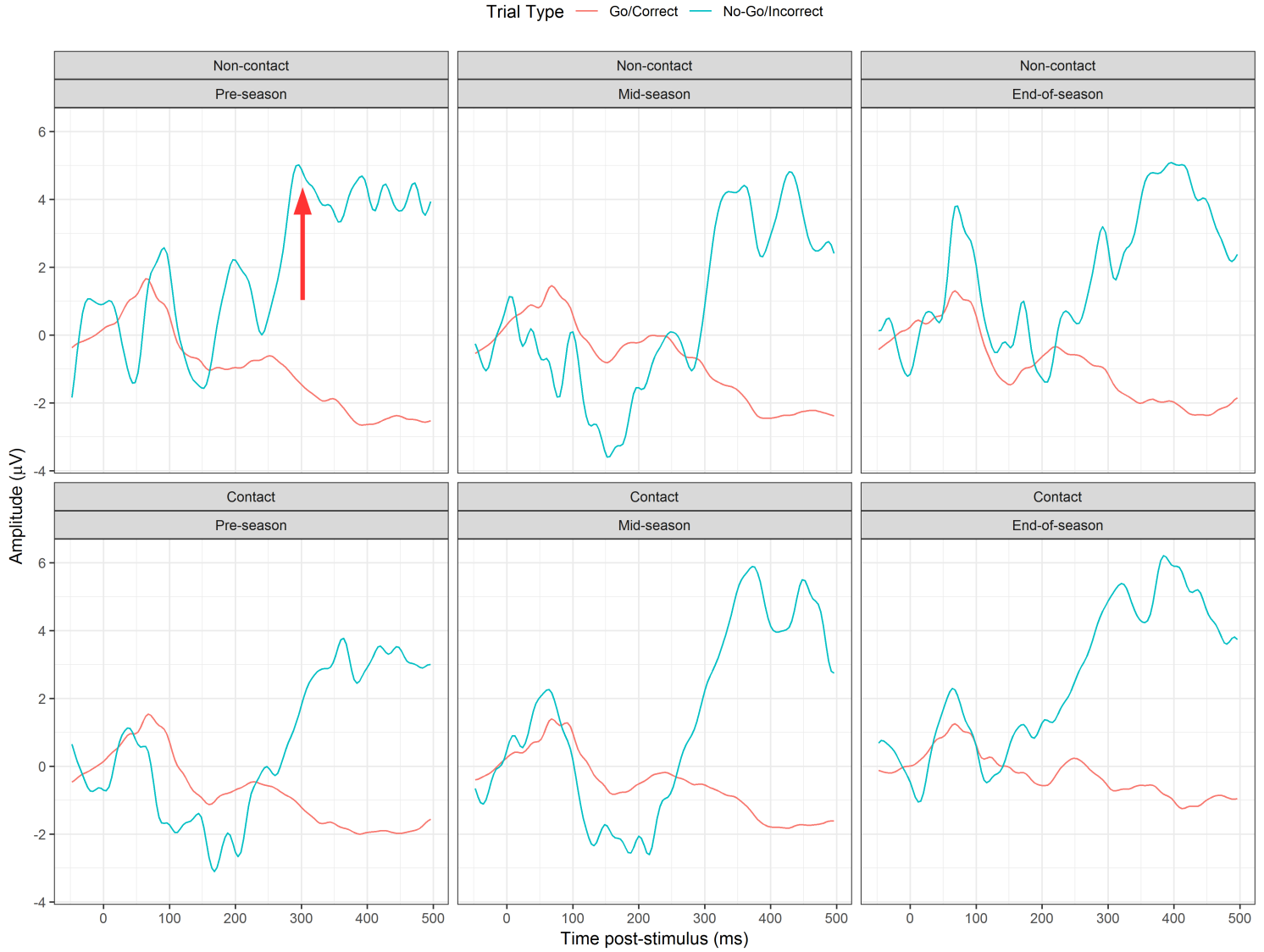

Figure 5.4: Post-Response Grand Average Waveforms (Pz).

Note: Grand average waveforms are presented for each group and each time point in the season at Pz. Red arrows denote an example of the Pe component. ERN is not noted in this figure since values were extracted from FPz and Fz.

5.4.2 CRN

Initial analyses revealed a trial type effect in ERN/CRN (Figure 5.5). Such that ERN amplitudes (incorrect responses) were larger in comparison to CRN amplitudes (correct responses), $t(190)$ = -6.08, $p < .001$.

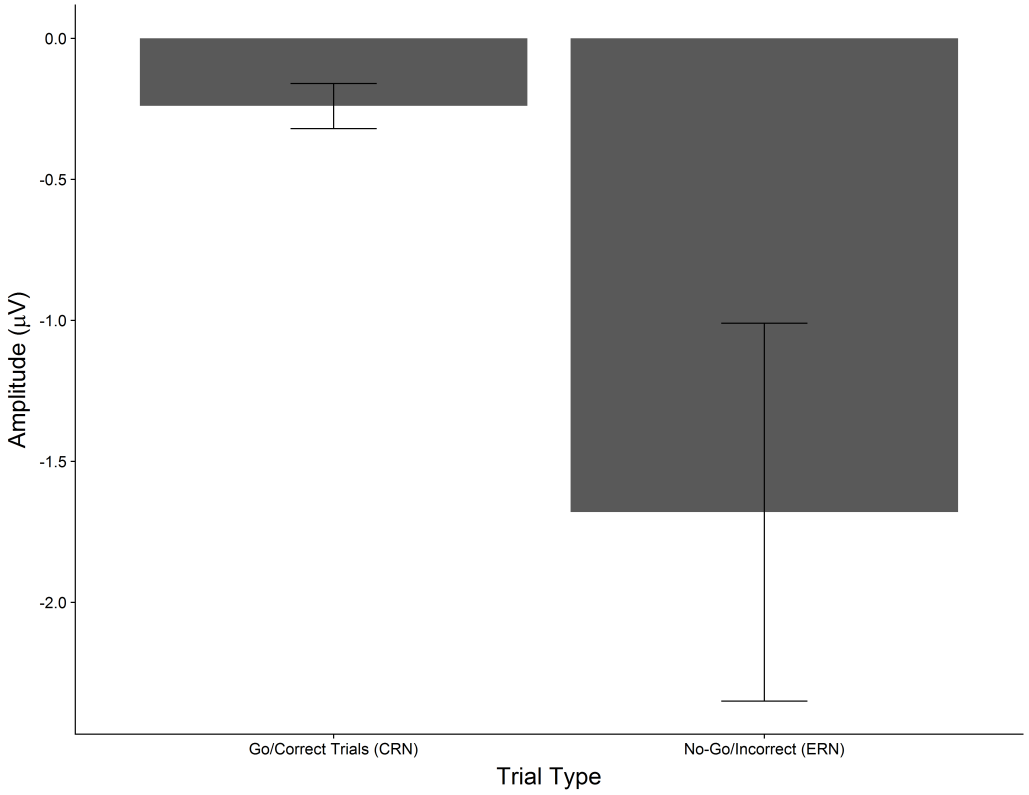

Figure 5.5: Post-Response Trial Type Differences in ERN/CRN

A three-way interaction between athlete type, number of prior concussions and time was observed in CRN amplitude during end-of-season measures was observed, $t(120)$ = -2.30, $p = .023$. Post-hoc analyses demonstrated that both contact and non-contact athletes displayed increases in CRN amplitude at end-of-season, $t(114)$ = -2.94, p = .004. Yet, contact-sport athletes without a concussion history showed greater increases in CRN peak amplitude over the course of the season in comparison to contact-sport athletes without a concussion history, $t(120) = 2.80$, $p = .006$. Concus-

sion history had the opposing effect on non-contact sport athletes over time (Figure 5.6. The number of undiagnosed concussions did not have any appreciable effect on measures of CRN amplitude (p>.05).

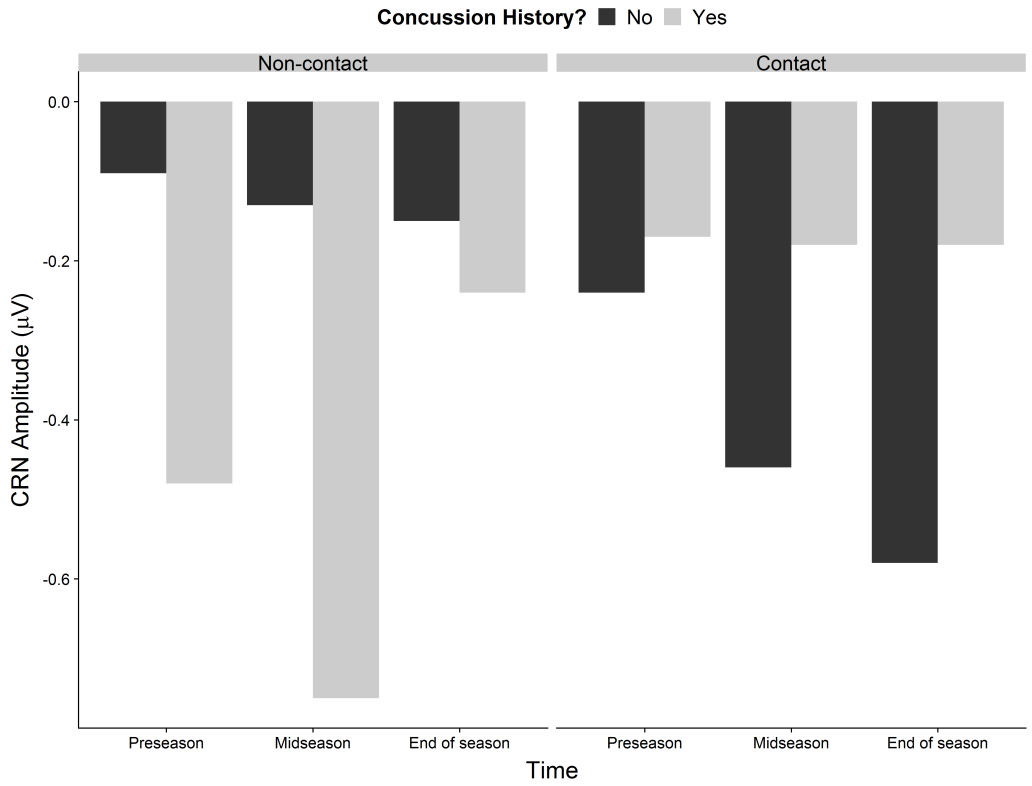

Figure 5.6: CRN Amplitude Changes Over Time in Contact and Non-Contact Athletes

5.4.2.1 Changes in CRN from Baseline in Contact Athletes

Change in ERP components from baseline were calculated at both mid-season and end-of-season. During the Go/Correct trials the change in CRN amplitude from baseline was associated with cumulative rotational acceleration measures as well as the largest linear and rotational acceleration experienced throughout the season. Such that, in contact athletes as peak linear acceleration increased CRN amplitude became increasingly positive (Figure 5.7), $t(8) = 3.80$, $p = .005$. The maximum number of

impacts over the course of the season also significantly affected CRN amplitude, $t(8) = 2.45$, $p = .040$, such that athletes with more impacts showed greater increases in CRN. Several cumulative metrics (rotational force, linear force, HITsp, GSI) failed to demonstrate any effect, regardless of the component or condition being examined.

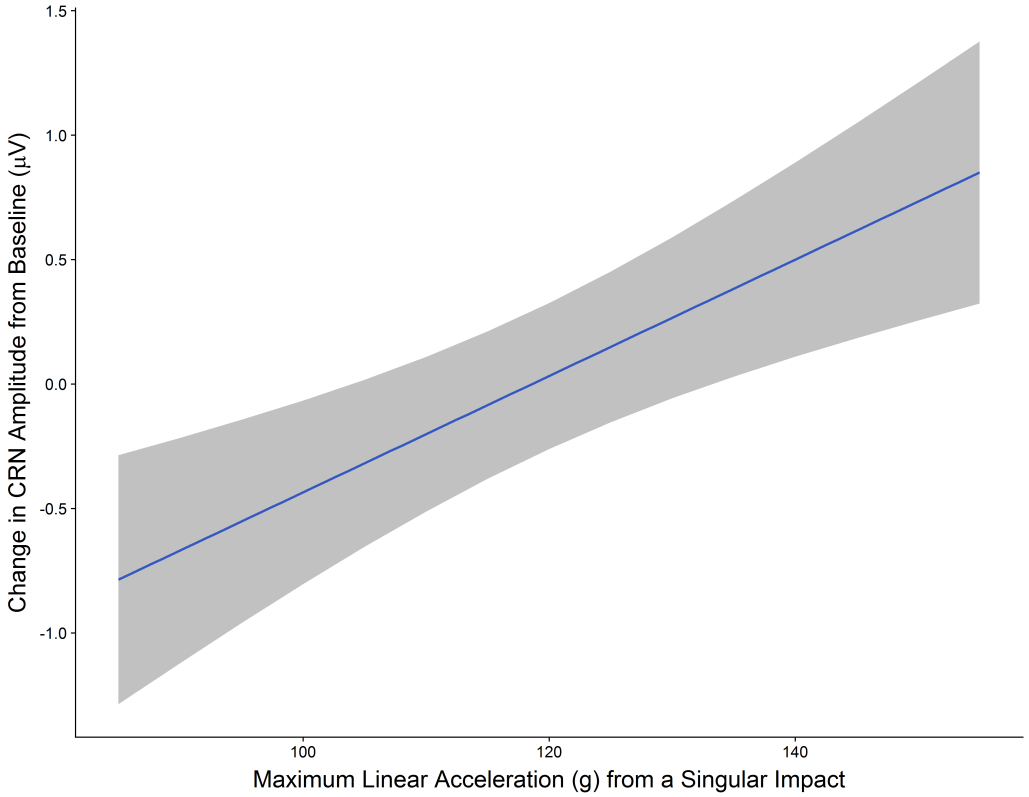

Figure 5.7: CRN Amplitude Changes as a Function of the Greatest Linear Acceleration from a Singular Impact

5.4.3 ERN

A significant main effect of undiagnosed concussions on ERN amplitude was observed, $t(19) = -2.20$, $p = .040$. Such that both contact and non-contact athletes with undiagnosed concussions showed attenuated ERN compared to athletes with no undiagnosed concussions. A separate model using total number of concussions (diagnosed and undiagnosed) failed to demonstrate the same level of significance (p=.067). These

differences are highlighted in Figure 5.8.

A three-way interaction between athlete type, history of undiagnosed concussions and ERN amplitude measures was observed at mid-season, $t(41) = 2.51$, $p = .016$ but was not present during end-of-season measures.

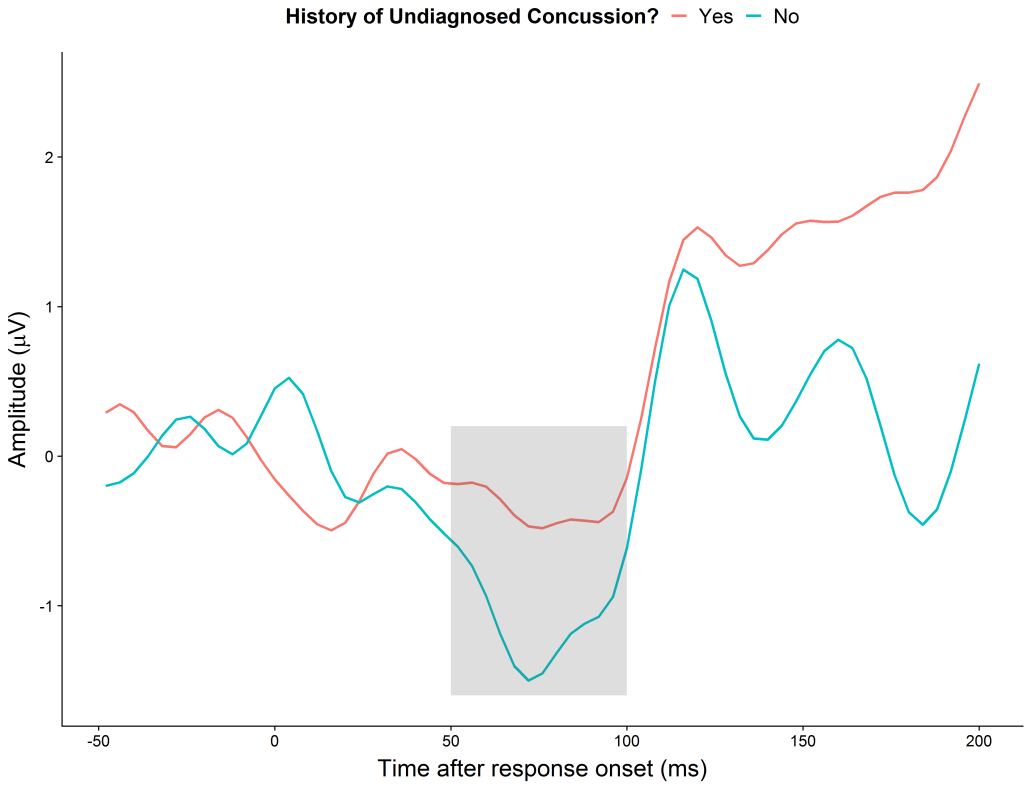

Figure 5.8: ERN Amplitude as a Function of Undiagnosed Concussion History

5.4.3.1 Changes in ERN from Baseline in Contact Athletes

During the incorrect response trials there was an interaction in ERN amplitude changes from baseline, linear impact density and concussion history, $t(10) = -2.35$, $p = .040$. Analyses of this interaction revealed that athletes with more concussions showed lower ERN amplitude as a function of increases in linear impact density.

5.4.4 Pe

A three way interaction in Pe amplitude between trial type, athlete type and undiagnosed concussions was observed, $t(180) = -4.21$, $p < .001$. Post-hoc analyses revealed that the Pe was greater during in incorrect responses. Additionally, during the correct trials there was no effect of athlete type or number of concussions on changes in Pe amplitude over the course of the season. However, during error trials, contact athletes with larger number of undiagnosed concussions showed significantly smaller Pe amplitude over the course of the season when compared to non-contact athletes.

Differences in Pe amplitude between athlete types presented themselves at mid-season, $t(60) = 3.36$, $p = .001$. Post-hoc analyses revealed that football athletes showed greater (more positive) Pe amplitudes at mid-season than non-contact athletes. This relationship was absent during end-of-season measures. An interaction between the number of undiagnosed concussions and athlete type was also observed, $t(20) = -2.39$, $p = .027$. Football athletes showed a linear decrease in Pe amplitude with increasing number of undiagnosed concussions while non-contact athletes showed no changes in Pe amplitude based on concussion history.

5.4.4.1 Changes in Pe from Baseline in Contact Athletes

A three way interaction in changes in Pe amplitude from baseline during incorrect responses between rotational impact density, concussion history and end of season measures was noted, $t(14) = 3.01$, $p = .009$. Similar results were found in linear impact density, $t(14) = 3.04$, $p = .009$. Analyses of the interaction demonstrated that athletes, who exceeded rotational impact density values of 1.3 rad/s/s/s or 0.03 g/s in linear impact density, had smaller Pe amplitudes at end of season compared to baseline as a function of their total number of concussions.

5.4.5 Results Summary

Table 5.2: Results Summary: Contact vs Non-Contact Athletes

Component	Test	Result	$R^2_{LMM(c)}$	$R^2_{LMM(m)}$
CRN/ERN amplitude	CRN/ERN×Trial Type	t(190)=-6.08, p<.001	0.36	0.49
CRN amplitude	Athlete Type×Concussion History×Time	t(120)=-2.30, p=.023	0.16	0.53
ERN amplitude	Undiagnosed Concussions	t(19)=-2.20, p=.040	0.15	0.46
Pe amplitude	Athlete type×Undiagnosed Concussions×Trial Type	t(180)=-4.21, p<.001	0.55	0.64

Note: $R^2_{LMM(c)}$: Conditional R^2; $R^2_{LMM(m)}$: Marginal R^2

Table 5.3: Results Summary: Head Impact Metrics in Contact Athletes

Component	Test	Result	$R^2_{LMM(c)}$	$R^2_{LMM(m)}$
CRN amplitude	Peak Linear Acceleration	t(8)=3.80, p=.005	0.19	0.39
CRN amplitude	Number of Impacts	t(8)=2.45, p=.040	0.05	0.41
ERN amplitude	Linear Impact Density×Concussion History	t(8)=-2.35, p=.040	0.27	1.00
Pe amplitude (NgI)	Linear Impact Density×Concussion History	t(14)=3.04, p=.009	0.64	0.69
Pe amplitude (NgI)	Rotational Impact Density×Concussion History	t(14)=3.01, p=.009	0.64	0.69

Note: $R^2_{LMM(c)}$: Conditional R^2; $R^2_{LMM(m)}$: Marginal R^2

5.5 Discussion

A recent fMRI study[273] was conducted to evaluate differences in resting-state fMRI between contact and non-athletes with concussion. The authors originally theorized that the benefits of exercise would exarcebate any significant decreases in function between groups. Despite their hypotheses, they found significant decreases in connectivity within the cingulate cortex (the proposed source generator of the ERN) within their athlete group. Based on their findings they hypothesized that repeated subclinical head impacts were responsible for the differences between groups. Given the location of their finding, the ERN was a prime candidate to further investigate these differences.

Previous investigations by Larson et al.[274] as well as De Beaumont et al.[265] and Pontifex et al.[253] all found decreases in ERN amplitude as a function of concussion. To our knowledge there has yet to be published studies evaluating changes in ERN in association with head impact metrics from telemetry systems. We drew inference from the aforementioned findings with concussion history and hypothesized that reduction in the ERN would be present (indicating detriments in error processing) within our football athletes which was partially confirmed.

As predicted, our data lends support to previous findings that the degree of attenuation in ERN/CRN amplitude and concussion history is linear[253,265]. These findings were consistent in both contact and non-contact athletes. Adding to this narrative we found a linear trend in ERN and Pe amplitude which decreased as a function of linear and rotational impact density in contact athletes. These findings indicate that error monitoring processes decrease as a function of both increases in select head impact metrics and concussion history.

The ability to differentiate between diagnosed and undiagnosed concussive injuries

has potential clinical utility particularly in high school athletes where the severity of injury may be underestimated[275]. In a study of 778 high-school athletes, Rivara et al.[276] reported that 69% of concussed athletes continued to play despite the presence of symptoms. Delayed reporting has been observed to increase recovery time following a concussion by nearly five days[277]. These findings are particularly alarming given recent reports that sports-related concussion rates continue to increase within this cohort[278]. In a multi-center study conducted by Meehan and colleagues[279] encompassing 486 athletes (age = 15.4 years), 30% of patients reported they had sustained a concussion which went undiagnosed. Undiagnosed concussions were associated with higher post-concussion symptom scale scores (PCSS) and higher loss of consciousness (LOC) rates with their current injury than athletes without previously undiagnosed concussions.

Meehan et al.[233] demonstrated unique effects of diagnosed and undiagnosed injuries using transcranial magnetic stimulation (TMS). Specifically, they found detriments in inhibitory network measures in participants who failed to have their injuries medically diagnosed during adolescence. Prior ERP investigations[253,265,274] evaluating changes in ERN amplitude failed to assess differences between diagnosed and undiagnosed concussive injuries.

Our results demonstrate that ERP components may have the ability to discriminate between diagnosed and undiagnosed injuries. Specifically, we observed that the ERN and Pe were more closely associated with the number of undiagnosed concussions while the CRN was associated with the total number of concussions (diagnosed and undiagnosed concussions). Adding to this narrative, in our secondary analyses of contact athletes and telemetry data, we reported linear trend in ERN and Pe amplitude which decreased as a function of linear and rotational impact density in contact athletes once a threshold was exceeded.

There are similarities between the compounding reduction in ERN amplitude as a function of head impact threshold and concussion history in our study and those described by Churchill et al.[280]. Their DTI investigation similarly reported larger alterations in contact-sport athletes with a concussion history which was expressed as a function of fractional anisotropy (FA). Upon first glance the results from our study and those reported by Churchill and colleagues would seem unrelated. However, in a study combining both ERN and FA[281], an index of myelination in white matter, a significant positive association between these measures was observed within the posterior cingulate region. Specifically, increasingly negative ERN values were associated with higher FA. Based on this report, it could be conceivably hypothesized that similar processes are being described despite using different neuroimaging modalities.

We also reported an association between decreases in error-related negativity (ERN) amplitude and peak linear acceleration, defined as the impact causing the largest linear acceleration throughout the entire season. While this is the first ERP study to demonstrate this relationship, changes in brain indices as a function of peak linear acceleration have been described alongside fMRI. Specifically, McAllister et al.[247] described an association between white matter changes in the amygdala and peak linear acceleration. Given prior work by Fein et al.[282] describing a strong link between lower amygdaloid volume and decision-making impairments, it is possible that findings reported here and those by McAllister et al.[247] are describing similar processes.

In contrast to our results, previous ERP studies have failed to demonstrate a consistent relationship between CRN and sports-related concussion. However, similar insights in CRN have been described in relation to declines in cognitive control due to aging[283]. Niessen and colleagues[283] reported an association between age and increases in undetected errors. Older adults in their study showed declines in Pe amplitude[283] as a function of undetected errors. Older adults also show similarly

sized ERN and CRN amplitudes[284] and smaller error potentials (ERN and Pe)[285].

The works in elderly population may lend support to the cognitive decline hypothesis of concussion[286]. Similar to the elderly participants in the aforementioned studies, amplitude differences between the ERN and CRN were attenuated in contact-sport athletes with a concussion history. Although similar parallels were also reported in Pe amplitude, in light of the absence of measures of error awareness provided by the Go/No-Go task, which is closely tied to this component[287,288], these results should be discussed with caution until further studies investigating the role of conscious awareness of errors are undertaken.

Collectively, results add to prior works which have demonstrated that changes in the brain may occur from head impacts without clinical presentation. Within our sample, event-related potentials were able to detect changes relative to head impact metrics. These results seem to align with prior fMRI research showing deficits in working memory and impulse control[247,280]. Our findings may present a foundation for future work with telemetry systems, ERP and fMRI measurements.

5.5.1 Limitations

Prior research[265] has utilized groups with 3 or more concussions, within our sample all athletes with a concussion history reported a maximum of 2 concussions. A wider range of undiagnosed concussions would be preferable to adequately discern its effect on ERP components and head impact metrics.

The effect of Pe amplitude may benefit from subsequent research utilizing a different task which allows for task certainty to be incorporated. As shown by prior work[288], differences in Pe amplitude vary greatly based on the awareness of the error being committed. Hence, difference in Pe amplitude should be interpreted with caution.

Within our study, participants were dropped from analyses due to limited number of trials. The use of another task or a larger number of trials may be preferable to view changes associated with certain components.

Differences in the number of impacts by football position (e.g. quarterback vs linebacker) were not evaluated due to the low sample size represented by each group. As previously stated, cumulative impact metrics may exhibit decreasing sensitivity when the amount of time between impacts incurred and electrophysiological measures are not properly controlled. As previously stated, cumulative impact metrics may exhibit decreasing sensitivity when the amount of time between impacts incurred and electrophysiological measures are not properly controlled. In contrast to our study which reported gaps between head impacts. Future work may wish take electrophysiological measurements closer to the last game of the season. Despite being the best option to measure head impact magnitude currently available, the inaccuracies of the HIT system should also be considered[289–291]. Despite its promise as a head impact metric, impact density is a novel measure which has yet to be independently validated. In our original study design, additional impact metrics were computed 24 hours, 3 days and 7 days prior to the ERP measurement date for mid-season and end of season. These included: the number of total head impacts, cumulative linear acceleration, cumulative rotational acceleration, HITsp, linear impact density and rotational impact density. Due to missing data these measures were not able to be investigated in this study.

5.6 Conclusion

Here we demonstrated that ERP components may prove useful in discriminating between diagnosed and undiagnosed concussive injuries, which may prove useful within

a clinical setting. Overall the results from this investigation demonstrate a significant association between head impacts that occurred over the course of a football season and measures of error monitoring and awareness. This association was only present in impact metrics which weigh the time between measurements and impacts.

CHAPTER 6

Summary and Future Directions

The results from this study demonstrate changes in electrophysiological measurements between football and non-contact athletes in as little as one season of exposure. The most notable changes were observed in N2 and P3 latency where contact athletes showed.

These changes, although statistically significant, are likely well below levels that could be used to ascertain clinical deficits. Future researchers should take extreme caution in distinguishing these levels of significance. The longitudinal course of these changes may, over years of exposures, reach levels of clinical significance. Based on this study, health-related quality of life measures are a poor measure of season to season changes from head impacts in sports.

The development of more accurate telemetry systems may help generate more consistent head impact metrics that could therein demonstrate consistent associations with other common measures of concussions which include but is not limited to: neuropsychological, motor control and/or general symptom assessments. Additionally, the application of more precise systems outside of American football should be encouraged.

Appendix

7.1 Appendix A

GUID_____ Subject Number_____ | 1

VISIT 1: BASELINE TESTING

Informed Consent

Specify the date the subject visited for baseline testing prior to start of season (MM/DD/YYYY)
_____/_____/_____

Specify the date on which the participant/subject (or the legal representative on behalf of the participant/subject) agrees to participate in a protocol, treatment, or other activity by signing an informed consent document
_____/_____/_____

Specify the type of informed assent/consent that was obtained ☐ Written ☐ Electronic ☐ Other

Did the subject provide informed assent (if <18 years) or consent (if >17)? ☐ Yes ☐ No ☐ Not applicable

If the subject is a minor (<18 years), was written informed parental consent obtained?
☐ Yes ☐ No

If applicable, what was the date of obtained assent? _____/_____/_____

Inclusion Criteria

Is the subject aged 14-26? ☐ Yes ☐ No

Is the subject currently symptomatic? ☐ Yes ☐ No

Does the subject express willingness to participate and is he/she able to give informed assent (child) and/or consent (parent for minors or adult 18+ of age for self)? ☐ Yes ☐ No

Is the subject a member of an organized athletic team or do they regularly train for and participate in independent athletic contests during at least one sports season? ☐ Yes ☐ No

Is the subject currently enrolled in a high school or college? ☐ Yes ☐ No

Exclusion Criteria

Is the subject bald or do they have dread locks/long, thick hair which precludes the appropriate scalp electrode fit?
☐ Yes ☐ No

What is the value for the subject's age, calculated as elapsed time since the birth of the participant/subject
_____

Does the subject currently have ADHD or have a history of ADHD? ☐ Yes ☐ No

Does the subject have an active head lice infection, open scalp wound, deafness or/and blindness?
☐ Yes ☐ No

Does the subject currently have or ever had a history of moderate or severe TBI (i.e., Glasgow Coma Scale <13), any brain injury with positive neuroimaging findings, or brain surgery? ☐ Yes ☐ No

Has the subject sustained a diagnosed concussion within the previous six months?
☐ Yes ☐ No

Demographics

Date the participant/subject was born _____/_____/_____

Specify the subject's natural sex ☐ Male ☐ Female

What is the subject's city of birth? _____

What is the subject's country of birth? ☐ United States ☐ Other _____

What is the subject's self-reported height in cm? _____

What is the subject's self-reported weight in kg? _____

What is the subject's laterality? ☐ Right-handed ☐ Left-handed

Category of race(s) the participant/ subject most closely identifies with

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Unknown
- ☐ Not reported
- ☐ Other_____

Category of ethnicity the participant/subject most closely identifies with

- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown
- ☐ Not reported

Text for the language the participant/subject speaks most often _____

Status of employment of participant/subject

- ☐ Working now
- ☐ Only temporarily laid off
- ☐ Sick leave or maternity leave
- ☐ Looking for work, unemployed
- ☐ Retired
- ☐ Disabled, permanently or temporarily
- ☐ Keeping house
- ☐ Student
- ☐ Unknown
- ☐ Other_____

Highest grade or level of school the participant's/subject's primary caregiver has completed or the highest degree he/she has received

- ☐ Never attended/Kindergarten only
- ☐ 1st grade
- ☐ 2nd grade
- ☐ 3rd grade
- ☐ 4th grade
- ☐ 5th grade
- ☐ 6th grade
- ☐ 7th grade
- ☐ 8th grade
- ☐ 9th grade
- ☐ 10th grade
- ☐ 11th grade
- ☐ 12th grade, no diploma
- ☐ High school diploma
- ☐ GED or equivalent
- ☐ Some college, no degree
- ☐ Associate degree: occupational, technical, or vocational program
- ☐ Associate degree: academic program
- ☐ Bachelor's degree (e.g., BA, AB, BS, BBA)
- ☐ Master's degree (e.g., MA, MS, MEng, MEd, MBA)
- ☐ Professional school degree (e.g., MD, DDS, DVM, JD)
- ☐ Doctoral degree (e.g., PhD, EdD)
- ☐ Unknown

Number of years of education the subject has completed _____

Status of participant's/subject's participation in school

- ☐ Going to school
- ☐ On vacation from school (between grades)
- ☐ Neither
- ☐ Unknown

Specify whether the subject is enrolled in high school or college

- ☐ High school
- ☐ College
- ☐ Other, please specify _____

What is the name of the institution the subject is enrolled in? _____

Has the subject ever repeated a year of school? ☐ Yes ☐ No

Has the subject ever skipped a year of school? ☐ Yes ☐ No

Has the subject ever received academic assistance? ☐ Yes ☐ No

High School Sport History

Did the subject play sports in high school (Grades 9-12)? ☐ Yes No

What sport did the subject participate in? (List primary sport first)
_____

How many years did the subject play? ☐ 1 ☐ 2 ☐ 3 ☐ 4

List all other sports and specify number of years played in high school (choose only 1-4 years)

Junior High School Sport History

Did the subject play sports in high school (Grades 6-8)? ☐ Yes No

What sport did the subject participate in? (List primary sport first) _____

How many years did the subject play? ☐ 1 ☐ 2 ☐ 3

List all other sports and specify number of years played in high school (choose only 1-3 years)

Elementary School Sport History

Did the subject play sports in high school (Grades 1-5)? ☐ Yes No

What sport did the subject participate in? (List primary sport first)
_____

How many years did the subject play? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

List all other sports and specify number of years played in high school (choose only 1-4 years)

Medical Screening

Condition	Yes	No	If "Yes," please specify	Year of diagnosis	Status Active	Status Inactive
Experience migraines						
Alcohol Abuse			Frequency (drinks/week):			
Drug Abuse			Drug type: Frequency (times/week):			
Regular medication use			Medication name: Frequency:			
Family history of migraine headache in a first degree (eg mother, father, sibling) relative?			Whom: Year of diagnosis for each relative:			
Been under general anesthesia			Number of times			
Takes non-prescription stimulants (e.g., caffeine, red bull, monster, etc.)			Frequency (times/day):			

Have you had one or more headaches in the last 3 months?	**Yes**	**No**
Has your migraine limited your ability to work, study, or do what you wanted to do?	**Yes**	**No**
If yes, has light bothered you while experiencing a headache or migraine?	**Yes**	**No**
If yes, has a migraine or headache resulted in nauseas or getting sick to your stomach?	**Yes**	**No**

Concussion History

Number of prior concussions	_____
The reliability of the reported injury date	☐ Verified ☐ Estimated ☐ Unknown
The point in time estimated as injury date and time ☐ Time that the participant/subject became symptomatic ☐ Time of first trauma activation	☐ Time of presentation to emergency department
Date (and time, if applicable and known) reported for onset of participant's/subject's symptoms	_____/_____/_____
Date (and time, if applicable and known) of arrival at the first hospital, if the participant/subject was transferred to the study center from another hospital	_____/_____/_____

Diagnosed Concussion

Number of times subject has been diagnosed with a concussion by a medical provider (i.e. MD, ATC, EMT, PA, Nurse, etc.,) in the past (not including current concussion). Injury may or may not have been sport related (e.g. auto accident)

	Specify the date the concussion was sustained	Approximate age at time of injury	Did the concussion result in loss of consciousness?	Specify the duration of unconsciousness (minutes)	Did the concussion result in post-traumatic amnesia?	Specify amnesia duration (min)	Duration of symptoms (days)
Injury #1			Yes No		Yes No		
Injury #2			Yes No		Yes No		
Injury #3			Yes No		Yes No		
Injury #4			Yes No		Yes No		
Injury #5			Yes No		Yes No		

Undiagnosed Concussion

Please use the following definition of concussion to answer the questions below

Definition of concussion: A concussion is a blow to your head that causes a variety of symptoms that may last for a short period of time, such as a few plays or minutes of a game, or a longer period of time. These symptoms may include any of the following:

- Headache
- Difficulty concentrating or focusing
- Feeling slowed down
- Dizziness or balance problems
- Nausea
- Fatigue / lack of energy
- Feeling like you're in a fog
- Irritable
- Drowsiness
- Forgetting things (before or after the injury)
- Sensitivity to light
- Loss of balance
- Sensitivity to noise
- Blurred vision

IMPORTANT: A) you can have a concussion without being "knocked out" or unconscious

B) Getting your "bell rung" and "clearing the cobwebs" is a concussion

Following a blow to the head, have the subject ever experienced any of the symptoms listed below or had a concussion that was not evaluated by a medical professional (eg Doctor, Athletic Trainer, EMT)

☐ **Yes** ☐ **No**

	Specify the date the concussion was sustained	**Approximate age at time of injury**	**Did the concussion result in loss of consciousness?**	**Specify the duration of unconsciousness (minutes)**	**Did the concussion result in post-traumatic amnesia?**	**Specify amnesia duration (min)**	**Duration of symptoms (days)**
Injury #1			Yes No		Yes No		
Injury #2			Yes No		Yes No		
Injury #3			Yes No		Yes No		
Injury #4			Yes No		Yes No		
Injury #5			Yes No		Yes No		

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

Health Behavior Inventory

	Never	Rarely	Sometimes	Often
I have trouble paying attention	0	1	2	3
I get distracted easily	0	1	2	3
I have a hard time concentrating	0	1	2	3
I have problems remembering what people tell me	0	1	2	3
I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

Head Impact Monitoring

What is the helmet make? ☐ Riddell ☐ Other_____

What is the helmet's model? ☐ Revolution Speed ☐ Other_____

How many seasons has the subject's helmet been in use? _____

What is the size of the subject's helmet?

☐ Small ☐ Large
☐ Medium ☐ Extra-Large

EEG/ERP

Were EEG/ERP measurements recorded? ☐ Yes ☐ No

What is the test session number: _____

What is the value for circumference of the subject's head (cm): _____

What EEG Net size was used? ☐ Small ☐ Medium ☐ Large

Specify the time the EEG recording started and ended (hh:mm) Start: _____ End: _____

What was the order the ERP tasks were conducted in? ☐ Oddball-GoNoGo ☐ GoNoGo-Oddball

Indicate level of Oddball task completion: ☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____ /_____ /_____, _____:_____ AM PM

#	Composite Scores	Score	Reaction Time (minutes)
1	Processing Speed		
2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____ /_____ /_____, _____:_____ AM PM

Trial #	Fall distance (cm)	Clinical Reaction Time (ms)
1	□□.□ cm	
2	□□.□ cm	
3	□□.□ cm	
4	□□.□ cm	
5	□□.□ cm	
6	□□.□ cm	
7	□□.□ cm	
8	□□.□ cm	

SCAT-3: Symptoms

	None	Mild		Moderate		Severe	
Headache:	0	1	2	3	4	5	6
"Pressure in head:"	0	1	2	3	4	5	6
Neck pain:	0	1	2	3	4	5	6
Nausea or vomiting:	0	1	2	3	4	5	6
Dizziness:	0	1	2	3	4	5	6
Blurred vision:	0	1	2	3	4	5	6
Balance problems:	0	1	2	3	4	5	6
Sensitivity to light:	0	1	2	3	4	5	6
Sensitivity to noise:	0	1	2	3	4	5	6
Feeling slowed down:	0	1	2	3	4	5	6
Feeling like "in a fog:"	0	1	2	3	4	5	6
"Don't feel right:"	0	1	2	3	4	5	6
Difficulty concentrating:	0	1	2	3	4	5	6
Difficulty remembering:	0	1	2	3	4	5	6
Fatigue or low energy:	0	1	2	3	4	5	6
Confusion:	0	1	2	3	4	5	6
Drowsiness:	0	1	2	3	4	5	6
Trouble falling asleep:	0	1	2	3	4	5	6
More emotional:	0	1	2	3	4	5	6
Irritability:	0	1	2	3	4	5	6
Sadness:	0	1	2	3	4	5	6
Nervous or anxious:	0	1	2	3	4	5	6

Total number of symptoms reported:	**Total symptom score:**
Do the symptoms get worse with physical activity?	☐ Yes ☐ No
Do the symptoms get worse with mental activity?	☐ Yes ☐ No
Cause of symptoms:	

Adverse Events

#	Adverse Event diagnosis, if known, or Signs/Symptoms (One sign/symptom per line)	Serious	Start date (mm/dd/yyyy)	Stop date or specify if ongoing (mm/dd/yyyy)	Severity	Relation to study procedure	Action taken	Outcome
1		Yes No						
2		Yes No						
3		Yes No						
4		Yes No						
5		Yes No						
6		Yes No						
7		Yes No						
8		Yes No						
9		Yes No						
10		Yes No						
					1-Mild 2-Moderate 3-Severe	1-Unrelated 2-Unlikely related 3-Possibly related 4-Probably related 5-Definitely related	1-None 2-Drug therapy 3-Study discontinued 4-Other (specify on comment box)	1-Resolved 2-Improved 3-Unchanged 4-Worsened

Protocol Deviations

Have any protocol deviations occurred? ☐ Yes ☐ No

#	Date of Deviation	CRF Page	Specify	Outcome
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Concomitant Medication/Treatment

Is the subject currently taking any medication/treatment? ☐ Yes ☐ No

#	Drug Name (generic name if possible)	Dose	Units	Frequency	Route	Indication	Therapy Start Date	Therapy End Date	Therapy Ongoing
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Frequency		Route	
QD = Every day	QID = Four Times a Day	PO = Oral	SC = Subcutaneous
QOD = Every other day	SID = Five Times a Day	TOP = Topical	INH = Inhalation
BID = Twice a Day	PRN = as needed	IV = Intravenous	PR = Per Rectum

TID = Three Times a Day	Other (Specify)	IM = Intramuscular	Other (Specify

Comments Page

Are there any comments to this form?

- ☐ Yes
- ☐ No

Page Number	Comment

VISIT 2: MID-SEASON EVALUATION

Specify the date the subject visited for testing (MM/DD/YYYY)	_____/_____/_____
What was the date of the first game?	_____/_____/_____
What was the date the season started?	_____/_____/_____

Adverse Events and Concomitant Medications

Did the subject experience any adverse events since the last visit?	☐ Yes ☐ No
Has the subject had any change in medications since the last visit?	☐ Yes ☐ No

Head Impact Monitoring

Head Impact System used (if applicable)		☐ HIT-System ☐ Estimation	
Number of practices	_____	Number of practice impacts	_____
Number of games	_____	Number of game impacts	_____
Total number of practices and games	_____	Total number of impacts	_____

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

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I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

EEG/ERP

Were EEG/ERP measurements recorded?	☐ Yes ☐ No
What is the test session number:	_____
What is the value for circumference of the subject's head (cm):	_____
What EEG Net size was used?	☐ Small ☐ Medium ☐ Large
Specify the time the EEG recording started and ended (hh:mm)	Start: End:
What was the order the ERP tasks were conducted in?	☐ Oddball-GoNoGo ☐ GoNoGo-Oddball
Indicate level of Oddball task completion:	☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____ /_____ /_____, _____:_____ AM PM

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2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____ /_____ /_____, _____:_____ AM PM

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3	□□.□ cm	
4	□□.□ cm	
5	□□.□ cm	
6	□□.□ cm	
7	□□.□ cm	
8	□□.□ cm	